Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
February 8, 2012

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anthelmintics
AHFS Class 080800
February 8, 2012

I. Overview

The anthelmintics are approved for the treatment of cestode, nematode and trematode infections.[1-6] Infections caused by helminths, or parasitic worms, are among the most prevalent infections in the world and are a leading cause of morbidity.[7] Helminths that parasitize humans are classified into cestodes (tapeworms), nematodes (roundworms) and trematodes (flukes).[7-8] Pinworm infections (*Enterobiasis vermicularis*) are the most common helminthic infections in the U.S., followed by *Ascaris lumbricoides*.[9]

Helminths vary with respect to life cycle, bodily structure, localization within the host, epidemiology, and susceptibility to chemotherapy.[8] The population density of the worm burden is an important factor in determining the pathogenicity of the infection.[10] Most infected persons harbor few worms and are asymptomatic or exhibit minimal signs or symptoms of disease.[7] However, persons with large numbers of worms are at risk for severe disease. Children infected with helminths are at risk of malnutrition, impaired growth, and impaired intellectual development. The diagnosis of helminthic infections is based primarily on microscopic examination of stool, urine, blood, other body fluids, and/or tissues.

The anthelmintics act locally to expel worms from the gastrointestinal tract. They also act systemically to eradicate adult helminths or developmental forms that invade organs and tissues.[8] Most human infections, caused by either flukes or intestinal helminths, may be cured or controlled by the available anthelmintic agents. Systemic infections caused by tissue-dwelling helminths may only partially respond to currently available drugs. Acquired resistance to anthelmintics in humans has yet to become a major factor limiting clinical efficacy.

The anthelmintic agents differ with regards to their mechanism of action.[1-6] Albendazole exhibits inhibitory effects on tubulin polymerization, which results in the loss of cytoplasmic microtubules. Ivermectin binds to glutamate-gated chloride ion channels leading to hyperpolarization of the nerve or muscle cell, which results in paralysis and death of the parasite. Mebendazole irreversibly blocks glucose uptake and other nutrients in susceptible adult intestine-dwelling helminths. Praziquantel induces a rapid contraction of schistosomes by affecting the permeability of the cell membrane, which causes vacuolization and disintegration of the schistosome tegument. Pyrantel pamoate is a depolarizing neuromuscular blocking agent, which paralyzes the parasite.

The anthelmintics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Mebendazole is available in a generic formulation and pyrantel pamoate is available over-the-counter. This class was last reviewed in August 2009.

Table 1. Anthelmintics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Albendazole	tablet	Albenza®	none
Ivermectin	tablet	Stromectol®	none
Mebendazole	chewable tablet	N/A	mebendazole
Praziquantel	tablet	Biltricide®	none
Pyrantel pamoate	suspension‡	Reese Pinworm®	Reese Pinworm®

‡Product is available over-the-counter.
PDL=Preferred Drug List
N/A=Not available

The anthelmintics have been shown to be active against the strains of organisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the anthelmintics that are noted in Table 4. These agents may also have been found to show activity to other organisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these organisms have not been established in adequate and well-controlled trials. Although empiric antiparasitic therapy may be initiated before diagnostic test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Anthelmintics[1-6]

Organism	Albendazole	Ivermectin	Mebendazole	Praziquantel	Pyrantel Pamoate
Cestodes (Tapeworms)					
Echinococcus granulosus	✔				
Taenia solium	✔				
Nematodes (Roundworms)					
Ancylostoma duodenale			✔		
Ascaris lumbricoides			✔		
Enterobius vermicularis			✔		✔
Necator americanus			✔		
Onchocerca volvulus		✔			
Strongyloides stercoralis		✔			
Trichuris trichiura			✔		
Trematodes (Flukes)					
Clonorchis sinensis				✔	
Opisthorchis viverrini				✔	
Schistosoma haematobium				✔	
Schistosoma japonicum				✔	
Schistosoma mansoni				✔	
Schistosoma mekongi				✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the anthelmintics are summarized in Table 3.

Table 3. Treatment Guidelines Using the Anthelmintics

Clinical Guideline	Recommendation(s)

Sanford Guide to Antimicrobial Therapy[11] (2011)	<u>Cestodes (Tapeworms)</u>
	• Hydatid Disease (*Echinococcus granulosus*)
	  o Meta-analysis supports percutaneous aspiration-injection-re-aspiration plus albendazole. Continue albendazole for 28 days.
	• Parenchymal Neurocysticercosis (*Taenia solium*)
	  o Primary: albendazole plus dexamethasone for 8-30 days and an anti-seizure medication
	  o Alternative: praziquantel plus dexamethasone for 29 days
	<u>Nematodes (Roundworms)</u>
	• Ascariasis (*Ascaris lumbricoides*)
	  o Primary: albendazole or mebendazole for 3 days
	  o Alternative: ivermectin for 1 dose
	• Hookworm (*Ancylostoma duodenale and Necator americanus*)
	  o Primary: albendazole for 3 days
	  o Alternative: mebendazole or pyrantel pamoate for 3 days
	• Onchocerciasis (*Onchocerca volvulus*)
	  o Primary: ivermectin administered as a single dose (repeated

Clinical Guideline	Recommendation(s)
	every 6 months) plus doxycycline for 6 weeks • Pinworm (*Enterobiasis vermicularis*) o Primary: mebendazole for 1 dose (repeat in 2 weeks) o Alternative: pyrantel pamoate or albendazole for 1 dose (repeat in 2 weeks) • Strongyloidiasis (*Strongyloides stercoralis*) o Primary: ivermectin for 2 days o Alternative: albendazole for 7 days, however is less effective than ivermectin • Whipworm (*Trichuriasis trichiura*) o Primary: albendazole for 3 days o Alternative: mebendazole or ivermectin for 3 days <u>Trematodes (Flukes)</u> • Liver Flukes o Primary: praziquantel for 2 days o Alternative: albendazole for 7 days • Schistosomiasis (all species) o Primary: praziquantel for 1 day
American Academy of Pediatrics (AAP): **Red Book: Report of the Committee on Infectious Diseases[12] (2009)**	<u>Cestodes (Tapeworms)</u> • Hydatid Disease (*Echinococcus granulosus*) o Drug of choice: albendazole for 1-6 months • Parenchymal Neurocysticercosis (*Taenia solium*) o Initial therapy for patients with inflamed parenchymal cysticercosis should focus on symptomatic treatment with anti-seizure medication. o Patients with live parenchymal cysts who have seizures should be treated with albendazole together with steroids and an anti-seizure medication. o Patients with subarachnoid cysts or giant cysts in the fissures should be treated for at least 30 days. o Surgical intervention or CSF diversion followed by albendazole and steroids is indicated for obstructive hydrocephalus. o Arachnoiditis, vasculitis or cerebral edema is treated with prednisone or dexamethasone together with albendazole or praziquantel. <u>Nematodes (Roundworms)</u> • Ascariasis (*Ascaris lumbricoides*) o Drug of choice: albendazole once, or mebendazole once, or ivermectin once • Hookworm (*Ancylostoma duodenale and Necator americanus*) o Drug of choice: albendazole once, mebendazole once, or pyrantel pamoate for 3 days • Onchocerciasis (*Onchocerca volvulus*) o Drug of choice: ivermectin once, repeated every 6-12 months • Pinworm (*Enterobiasis vermicularis*) o Drug of choice: mebendazole once, pyrantel pamoate once, or albendazole once (repeat in 2 weeks) • Strongyloidiasis (*Strongyloides stercoralis*) o Drug of choice: ivermectin for 2 days o Alternative: albendazole for 7 days • Whipworm (*Trichuriasis trichiura*) o Drug of choice: mebendazole once o Alternative: albendazole or ivermectin for 3 days <u>Trematodes (Flukes)</u>

Clinical Guideline	Recommendation(s)

	• Liver Flukes
	  o *Clonorchis sinensis*
	  ▪ Drug of choice: praziquantel for 2 days or albendazole for 7 days
	  o *Opisthorchis viverrini*
	  ▪ Primary: praziquantel for 2 days
	• Schistosomiasis (all species)
	  o Drug of choice: praziquantel for 1 day

Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines: Management of Encephalitis[23] (2008)**	<u>Empirical Therapy</u> • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. <u>Helminths</u> • *Baylisascaris procyonis:* albendazole plus diethycarbamazine can be considered; adjunctive corticosteroids should also be considered • *Gnathostoma* species: albendazole or ivermectin is recommended • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative
Center for International Blood and Marrow Transplant Research (CIBMTR)/National Marrow Donor Program (NMDP)/European Blood and Marrow Transplant Group (EBMT)/American Society of Blood and Marrow Transplantation (ASBMT)/ Canadian Blood and Marrow Transplant Group (CBMTG)/ Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA)/Association of Medical Microbiology and Infectious Diseases Canada (AMMI)/Centers for Disease Control and Prevention (CDC): **Guidelines for Preventing Infectious Complications Among Hematopoietic Stem Cell Transplantation Recipients: A Global Perspective[13] (2009)**	• Hematopoietic stem cell transplant (HSCT) candidates with pretransplant screening tests positive for *Strongyloides* species, or those with an unexplained eosinophilia and a travel or residence history indicative of exposure to *Strongyloides stercoralis*, should be empirically treated before transplantation. • The preferred prophylactic treatment is ivermectin 200 mcg/kg/day orally for 2 consecutive days; this regimen is repeated after 2 weeks. • The alternative prophylactic treatment is albendazole 400 mg orally twice daily for 7 days or thiabendazole 25 mg/kg orally twice daily for 2 days. • Some clinicians advocate preemptive treatment for patients from endemic areas who have no symptoms, no eosinophilia, and negative screening test results. • Indications for empiric treatment for strongyloidiasis before HSCT are the same among children or adults, except for children weighing <15 kg, for whom the preferred drug is thiabendazole.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the anthelmintics are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Anthelmintics[1-6]

Indication	Albendazole	Ivermectin	Mebendazole	Praziquantel	Pyrantel Pamoate
Cestodes (Tapeworms)					
Cystic hydatid disease of the liver, lung, and peritoneum	✔ *				
Parenchymal neurocysticercosis due to active lesions	✔				
Nematodes (Roundworms)					
Onchocerciasis		✔			
Strongyloidiasis of the intestinal tract		✔			
Ascariasis (*Ascaris lumbricoides*)			✔		
Hookworm (*Ancylostoma duodenale and Necator americanus*)			✔		
Pinworm (*Enterobiasis vermicularis*)			✔		✔
Whipworm (*Trichuriasis trichiura*)			✔		
Trematodes (Flukes)					
Clonorchiasis (liver flukes)				✔	
Opisthorchiasis (liver flukes)				✔	
Schistosomiasis, all species				✔	

*When medically feasible, surgery is considered the treatment of choice.

IV. Pharmacokinetics

The pharmacokinetic parameters of the anthelmintics are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Anthelmintics[1-6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Albendazole	<5	70	Liver	Renal (<1)	8-12
Ivermectin	Well absorbed	93	Liver	Renal (<1) Feces	18
Mebendazole	2-10	95	Liver	Renal (5-10) Feces (90-98)	1-11.5
Praziquantel	80	80	Liver	Renal (80)	0.8-3
Pyrantel pamoate	Partially absorbed	Not reported	Liver	Renal (<7) Feces (>50)	Not reported

V. Drug Interactions

Significant drug interactions with the anthelmintics are listed in Table 6.

Table 6. Significant Drug Interactions with the Anthelmintics[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Praziquantel	2	CYP 3A4 inducing anticonvulsants	CYP3A4 inducing anticonvulsants (phenytoin, phenobarbital, and carbamazepine) may increase the metabolism of praziquantel, resulting in reduced plasma levels and possible loss of therapeutic effect.
Praziquantel	2	Rifamycins	Rifamycins may increase the hepatic metabolism of praziquantel, resulting in reduced plasma levels and possibly producing a loss in therapeutic effect.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the anthelmintics are listed in Table 7. At recommended dosages, the anthelmintics are generally well tolerated. Some adverse effects may be secondary to the parasitic infection being treated and/or to dead and dying parasites rather than to the drug itself. Such effects may be more frequent and/or severe in patients with a heavy worm burden. Cutaneous and/or systemic reactions of varying severity (Mazzotti reaction) and ocular effects may occur in patients with onchocerciasis receiving macrofilaricidal drugs, such as ivermectin. Patients with onchocerciasis who are also heavily infected with *Loa loa* may develop serious or fatal neurologic events (e.g., encephalopathy and coma) either spontaneously or following rapid killing of microfilariae with macrofilaricidal agents.

Table 7. Adverse Drug Events (%) Reported with the Anthelmintics[1-6]

Adverse Events	Albendazole	Ivermectin	Mebendazole	Praziquantel	Pyrantel Pamoate
Cardiovascular					
Arrhythmia	-	-	-	✔	-
Chest discomfort	-	<1	-	-	-
Dyspnea	-	<1	-	-	-
Facial edema	-	1	-	-	-
Hypotension	-	<1	-	-	-
Orthostatic hypotension	-	1	-	-	-
Peripheral edema	-	✔	-	-	-
Tachycardia	-	4	-	-	-
Central Nervous System					
Asthenia	-	<1	-	✔	-
Coma	-	✔	-	-	-
Confusion	-	✔	-	-	-
Dizziness	1	3	✔	✔	✔
Drowsiness	-	✔	✔	-	✔
Fatigue	-	<1	-	-	-
Fever	1	-	-	✔	-
Headache	1-11	<1	✔	✔	✔
Increased intracranial pressure	0-2	-	-	-	-
Insomnia	-	-	-	-	✔
Lethargy	-	✔	-	-	-
Malaise	-	-	-	✔	-

Adverse Events	Albendazole	Ivermectin	Mebendazole	Praziquantel	Pyrantel Pamoate
Meningeal signs	1	-	-	-	-
Mental status changes	-	✔	-	-	-
Seizures	-	✔	✔	✔	-
Somnolence	-	<1	-	✔	-
Stupor	-	✔	-	-	-
Tremor	-	✔	-	-	-
Vertigo	1	<1	-	✔	-
Dermatological					
Alopecia	<1-2	-	-	-	-
Erythema multiforme	✔	-	-	-	-
Pruritus	-	3	-	✔	-
Rash	<1	<1	✔	-	✔
Stevens-Johnson syndrome	✔	✔	-	-	-
Toxic epidermal necrolysis	-	✔	-	-	-
Urticaria	<1	<1	✔	✔	-
Gastrointestinal					
Abdominal cramping	-	-	-	-	✔
Abdominal pain	0-6	<1	✔	✔	✔
Anorexia	-	<1	-	✔	✔
Constipation	-	<1	-	-	-
Diarrhea	-	2	✔	✔	✔
Fecal incontinence	-	✔	-	-	-
Nausea	4-6	2	✔	-	✔
Vomiting	4-6	<1	✔	✔	✔
Genitourinary					
Acute renal failure	✔	-	-	-	-
Glomerulonephritis	-	-	✔	-	-
Hematuria	-	-	✔	-	-
Urinary incontinence	-	✔	-	-	-
Hematologic					
Anemia	-	✔	✔	-	-
Agranulocytosis	<1	-	✔	-	-
Aplastic anemia	✔	-	-	-	-
Bone marrow suppression	✔	-	-	-	-
Eosinophilia	-	3	✔	✔	-
Hemoglobin increased	-	1	-	-	-
Granulocytopenia	<1	-	-	-	-
Leukopenia	<1	✔	✔	-	-
Neutropenia	✔	-	✔	-	-
Pancytopenia	<1	-	-	-	-
Thrombocytopenia	<1	-	-	-	-
Hepatic					
Abnormal liver function tests	1-16	2	✔	-	✔
Acute liver failure	✔	-	-	-	-
Hepatitis	✔	-	✔	-	-
Hyperbilirubinemia	-	✔	-	-	-
Musculoskeletal					
Back pain	-	✔	-	-	-
Myalgia	-	<1	-	✔	-
Neck pain	-	✔	-	-	-
Weakness	-	-	-	-	✔
Special Senses					
Abnormal eye sensation	-	✔	-	-	-

Adverse Events	Albendazole	Ivermectin	Mebendazole	Praziquantel	Pyrantel Pamoate
Anterior uveitis	-	✔	-	-	-
Chorioretinitis	-	✔	-	-	-
Choroiditis	-	✔	-	-	-
Conjunctival hemorrhage	-	✔	-	-	-
Conjunctivitis	-	✔	-	-	-
Eyelid edema	-	✔	-	-	-
Keratitis	-	✔	-	-	-
Ocular limbitis	-	4-6	-	-	-
Ocular punctate opacity	-	✔	-	-	-
Red eye	-	✔	-	-	-
Other					
Angioedema	-	1	✔	-	-
Asthma exacerbation	-	✔	-	-	-
Hypersensitivity reaction	<1	-	✔	✔	-
Mazzotti-type reaction	-	>10	-	-	-

✔ Percent not specified
\- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the anthelmintics are listed in Table 8.

Table 8. Usual Dosing Regimens for the Anthelmintics[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Albendazole	Hydatid Disease: <60 kg: 15 mg/kg/day given in divided doses twice daily with meals, with a maximum total daily dose of 800 mg (28-day cycle followed by a 14-day albendazole-free interval, for a total of 3 cycles) ≥60 kg: 400 mg twice daily with meals (28-day cycle followed by a 14-day albendazole-free interval, for a total of 3 cycles) Neurocysticercosis: <60 kg: 15 mg/kg/day given in divided doses twice daily with meals, with a maximum total daily dose of 800 mg, for 8-30 days ≥60 kg: 400 mg twice daily with meals for 8-30 days	Hydatid Disease: <60 kg: 15 mg/kg/day given in divided doses twice daily with meals, with a maximum total daily dose of 800 mg (28-day cycle followed by a 14-day albendazole-free interval, for a total of 3 cycles) ≥60 kg: 400 mg twice daily with meals (28-day cycle followed by a 14-day albendazole-free interval, for a total of 3 cycles) Neurocysticercosis: <60 kg: 15 mg/kg/day given in divided doses twice daily with meals, with a maximum total daily dose of 800 mg, for 8-30 days ≥60 kg: 400 mg twice daily with meals for 8-30 days	Tablet: 200 mg
Ivermectin	Onchocerciasis: A single oral dose designed to provide approximately 150 mcg of ivermectin per kg of body weight; retreatment may be considered at intervals as short	Onchocerciasis: ≥15 kg: A single oral dose designed to provide approximately 150 mcg of ivermectin per kg of body weight; retreatment may be	Tablet: 3 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	as 3 months Strongyloidiasis: A single oral dose designed to provide approximately 200 mcg of ivermectin per kg of body weight; In general, additional doses are not necessary.	considered at intervals as short as 3 months Strongyloidiasis: ≥15 kg: A single oral dose designed to provide approximately 200 mcg of ivermectin per kg of body weight; In general, additional doses are not necessary	
Mebendazole	Hookworm: 100 mg twice daily for 3 consecutive days Pinworm: 100 mg once; repeat in 2 weeks if necessary Roundworm: 100 mg twice daily for 3 consecutive days Whipworm: 100 mg twice daily for 3 consecutive days	Hookworm: ≥2 years of age: 100 mg twice daily for 3 consecutive days Pinworm: ≥2 years of age: 100 mg once; repeat in 2 weeks if necessary Roundworm: ≥2 years of age: 100 mg twice daily for 3 consecutive days Whipworm: ≥2 years of age: 100 mg twice daily for 3 consecutive days	Chewable tablet: 100 mg
Praziquantel	Clonorchiasis, Opisthorchiasis: 25 mg/kg 3 times per day as a one day treatment Schistosomiasis: 20 mg/kg 3 times per day as a one day treatment	Clonorchiasis, Opisthorchiasis: ≥4 years of age: 25 mg/kg 3 times per day as a one day treatment Schistosomiasis: ≥4 years of age: 20 mg/kg 3 times per day as a one day treatment	Tablet: 600 mg
Pyrantel pamoate	Pinworm: 11 mg/kg given as a single dose; maximum 1 gram. Repeat after 2 weeks.	Pinworm: 11 mg/kg given as a single dose; maximum 1 gram. Repeat after 2 weeks.	Suspension: 144 mg/ml

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the anthelmintics are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Anthelmintics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cestodes (Tapeworms)				
Chaurasia et al.[16] (2010) Albendazole 15 mg/kg/day for 3 days vs placebo	RCT, DB, PC Patients with new onset seizures and solitary cysticercus granuloma (neurocysticercosis)	N=67 6 months	Primary: Resolution of lesion on CT scan, seizure control at 6 months	Primary: Complete resolution of lesions in the albendazole group was 84.8% compared to 41.2% in the placebo group (P=0.001). Partial resolution of lesions occurred in 6% of albendazole patients compared to 11.8% of placebo patients (P=0.06) Seizures occurred in 9.1% of albendazole patients and 2.9% of placebo treated patients (P=0.239).
Wen et al.[18] (1994) Albendazole (ABZ) 15-20 mg/kg/day orally, for 30 days with intervals of 10 days between treatments for 3-6 courses (12-18 courses for multi-organ CE and AE) vs albendazole and surgery vs surgery	OL Patients with cystic echinococcosis (CE) or alveolar echinococcosis (AE) in China	N=178 3-7 years	Primary: Endocyst collapse rate, protoscolex viability, cyst wall pathology, clinical symptoms and signs Secondary: Side effects	Primary: Twenty-seven of 34 cysts (79.4%) in patients treated with ABZ and surgery showed increased necrotic changes and decreased viability of the cysts compared to the surgery group (P<0.001). However, 10 of 84 (11.9%) cysts in the surgery group showed spontaneous evidence of necrosis at surgery. ABZ treatment alone was successful in 14 (24.1%) patients, resulted in improvement in 29 (50%) patients and had no effect in 15 (25.9%) patients. Seven of the AE patients treated with ABZ and surgery showed improvement, with hydatid masses diminished or disappeared, jaundice subsided, and appetite and energy regained. Of the remaining seven patients who continued to receive ABZ for 6-15 more courses, 4 stabilized, and 3 deteriorated of which 2 died. Of the 5 AE patients receiving ABZ alone, 1 improved, 2 stabilized, and 2 deteriorated of which 1 died. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Side effects were reported in 18.4% of patients receiving ABZ and were primarily gastrointestinal symptoms (diarrhea, nausea, abdominal pain and vomiting) and transient elevation of serum transaminase levels. ABZ was withdrawn in 1 patient after 1 week of therapy due to intolerable itch.
Bildik et al.[50] (2007) Albendazole 10 mg/kg twice daily prior to surgery (group I=1 month; group II=2 months; group III=3 months) vs no preoperative therapy	RCT Patients with isolated hydatid cysts of the liver	N=84 3 months	Primary: Clinical signs of disease	Primary: Thirty-five percent of the patients showed no clinical signs of the disease. Sixty-two percent had tenderness in the right hypochondrium, 34.5% had hepatomegaly, and 30% had palpable mass. Following treatment with albendazole, scoleces were alive in 47.6% of patients in group I, 33.3% of patients in group II, and 0.9% of patients in group III. In the control group, 80% of patients' scoleces were intact. When group III was compared with the control group, a significant difference was observed (P<0.05). There was a significant difference between the groups when groups I and II were compared with group III.
Del Brutto et al.[19] (2006) Albendazole vs praziquantel vs placebo vs no therapy	MA Patients with neurocysticercosis	N=942 (11 trials) Variable duration	Primary: Resolution of cystic lesions, risk of seizure recurrence, frequency of seizures Secondary: Effect of corticosteroids on cysticidal drug efficacy, adverse events	Primary: Cysticidal drug therapy was associated with complete resolution of cystic lesions (44% vs 19%; P=0.025). Trials on enhancing lesions showed a trend toward lesion resolution favoring the use of cysticidal drugs (72% vs 63%; P=0.38) that became statistically significant when an outlier trial was excluded from the analysis (69% vs 55%; P=0.006). Risk for seizure recurrence was lower after cysticidal treatment in patients with enhancing lesions (14% vs 37%; P<0.001). The single trial evaluating the frequency of seizures in patients with cystic lesions showed a 67% reduction in the rate of generalized seizures with treatment (P=0.006). This meta-analysis did not further analyze and compare the efficacy or safety of albendazole to praziquantel.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Only 1 study compared the efficacy of cysticidal drugs alone or in combination with corticosteroids, showing that albendazole plus dexamethasone was not better than albendazole alone in terms of lesion resolution (74% vs 76%) or risk of seizure recurrence during follow-up (12% vs 14%). Data from the trials did not allow an evaluation of the exact number of patients developing adverse events, but these manifestations generally were mild and resolved with analgesics or other symptomatic medications in a few days. The occurrence of adverse events did not differ between albendazole or praziquantel, or whether the patient received routine corticosteroids.
Das et al.[49] (2007) Group A Albendazole 15 mg/kg/day for 14 days plus dexamethasone 2 mg every 8 hours or 14 days, plus antiepileptic drugs vs Group B Antiepileptic drugs plus placebo	RCT Patients with newly diagnosed neurocysticercosis with more than one lesion detected on contrast head CT imaging	N=300 8 years	Primary: Recurrence of seizures, encephalopathy, need for subsequent hospital admission, death, resolution of lesions on follow-up CT	Primary: During the first year of treatment the incidences of seizure, encephalopathy, and readmission were greater for group A than group B (P=0.05; 95% CI 0.20–0.34 for group A and 0.10–0.22 for group B). Two patients in group A died from intractable seizures and encephalopathy in the first 3 months of treatment. For every follow-up point after 1 year of treatment, the incidences of seizure and need for readmission were also marginally higher in group A, but the differences were not statistically significant. Over the entire study period, the proportion of patients with complete resolution of lesions was greater in group B than in group A (P=0.05; 95% CI 0.56–0.57 in group A and 0.72–0.74 in group B), but the proportion of patients with calcification of lesions was greater in group A than in group B (P=0.05; 95% CI 0.33–0.34 in group A and 0.22–0.23 in group B).
Carpio et al.[48] (2008) Albendazole 400 mg every 12 hours (>50kg) or	DB, RCT, PC Patients of any age or gender with new onset of symptoms associated with	N=178 1 year	Primary: Disappearance of active cysts by 12 months of follow-up	Primary: Active cysts were identified in 69% of the albendazole treatment group and 66% of the placebo group. By 12 months following treatment, 38% of those with 12 month scans were free of active cysts in the treatment group compared with 20% in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
15mg/kg/day (<50kg) for 8 days vs placebo All patients received prednisone; anticonvulsants were allowed for patients with newly occurring seizures	neurocysticercosis (NC) and active and/or transitional NC cysts (Ecuador)		Secondary: Disappearance of transitional or calcified cysts at 1, 6 and 12 months, change in number of cysts in a specific phase, time to seizure recurrence, and adverse events	placebo group (P=0.048). Secondary: The difference in cyst disappearance by treatment was greatest at 1 month of follow-up, with 31% of those in the albendazole group being free of active cysts at month 1 of follow-up compared with 7% of those in the placebo group (P=0.001). Of those patients followed and scanned at 6 months, 35% were free of active cysts in the albendazole treatment arm compared with 12% in the placebo group (P=0.006). The mean number of active cysts decreased between baseline and month 1 for the ALB (mean number at baseline 3.88 and at 1 month 1.86) group but not for the placebo group (mean at baseline 2.67 and at 1 month 2.69). Those taking albendazole had a significant decrease in the number of active cysts between baseline and month 1 compared with those in the placebo group (P=0.001). There was no difference by treatment group in the change in the number of active cysts between month 1 and month 6 (P=0.797) or month 6 and month 12 of follow-up (P=0.938). The change in the number of transitional cysts and inactive calcifications between baseline and month 1 of follow-up did not differ by treatment group (transitional cysts P=0.234; calcifications P=0.456). The mean time seizure free was 8.86 months in the albendazole group versus 7.67 months in the placebo group (P=0.274). The three most common symptoms reported during treatment and the first month following treatment were headache, seizures and stomach problems. During the 8 days of treatment, three patients developed intracranial hypertension, all in the placebo group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kaur et al.[14] (2009) Albendazole 15 mg/kg/day in 3 divided doses for 7 days, plus prednisolone 2 mg/kg/day for 5 days, plus praziquantel 75 mg/kg/day in 3 divided doses for 1 day vs albendazole 15 mg/kg/day in 3 divided doses for 7 days, plus prednisolone 2 mg/kg/day for 5 days, plus placebo	RCT, DB, PC Children 1 to 13 years of age with seizures due to neurocysticercosis	N=112 1 year	Primary: Recurrence of seizure and resolution of lesions on CT	Primary: Resolution of lesions at 1, 3, and 6 months was higher in the praziquantel group (35%, 60%, 72%, respectively) compared to those receiving placebo (25%, 42% and 52%, respectively), but this did not reach statistical significance. Non-resolution and calcification at 1, 3, and 6 months were numerically lower in the praziquantel group compared to placebo; however, this was not significant. Recurrence of seizures within 6 months of therapy was reported in 3 children in each treatment group. There were no signs of elevated intracranial pressure.
Nematodes (Roundworms)				
Belizario et al.[20] (2003) Albendazole 400 mg as a single dose vs ivermectin 200 mcg/kg as a single dose	PC, RCT, SB Children in an elementary school in the Philippines infected with *Ascaris lumbricoides* and/or *Trichuris trichiura*	N=784 1 year	Primary: Cure and infection rates, egg counts	Primary: Albendazole, ivermectin and the drug combinations gave significantly higher cure and egg reduction rates for ascariasis than diethylcarbamazine (P<0.001). Infection rates were significantly higher at day 180 with diethycarbamazine (P<0.001); however, there were no significant differences between treatments on day 360. Albendazole, ivermectin and albendazole plus ivermectin produced cure rates of 69.7%, 78.4% and 78.1%, respectively. For trichuriasis, albendazole plus ivermectin produced significantly higher cure rates (P<0.001) and egg reduction rates (P<0.001) than other treatments. Albendazole plus ivermectin produced the lowest infection

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs diethylcarbamazine 150 mg as a single dose vs albendazole 400 mg and diethylcarbamazine 150 mg as a single dose vs albendazole 400 mg and ivermectin 200 mcg/kg as a single dose				rates on days 180 and 360 (P<0.001). Albendazole, ivermectin and albendazole plus ivermectin produced cure rates of 31.5%, 35.1% and 65.1%, respectively.
Muchiri et al.[21] (2001) Albendazole 600 mg at 6 month intervals vs mebendazole 600 mg at 4 or 6 month intervals	DB, RCT Children ages 4 to 19 years with *Ascaris lumbricoides*, *Trichuris trichiura* and/or hookworm infections in West Kenya	N=1,186 1 year	Primary: Cure rate, egg reduction	Primary: The cure rates for albendazole were 92.4% for hookworm infection, 83.5% for *A lumbricoides*, and 67.8% for *T trichiura*. Mebendazole given either 2 or 3 times in a year had cure rates of 50.0% and 55.0%, respectively, for hookworm, 79.6% and 97.5% for *A lumbricoides*, and 60.6% and 68.3% for *T trichiura* infection. Albendazole was significantly more effective than either regimen of mebendazole for treating hookworm infections (P<0.0001). Three doses of mebendazole were more effective against *A lumbricoides* than 2 doses of albendazole (P<0.0001). The cure rate for *T trichiura* by mebendazole given at 4-month intervals was higher than the 6-month regimen (P=0.035), but comparable to albendazole given at 6-month intervals. The geometric mean intensity of hookworm eggs per gram (epg) of stool decreased by 96.7% after albendazole treatment compared with 66.3% and

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				85.1%, respectively, for 2 or 3 doses of mebendazole (P<0.05) over the same period. Reductions in epg for *A lumbricoides* and *T trichiura* were comparable for both drugs.
Legesse et al.[22] (2002) Albendazole 400 mg as a single dose vs mebendazole 100 mg BID for 3 days	RCT Patients with single or mixed *Ascaris lumbricoides* and/or *Trichuris trichiura* infections	3 days	Primary: Cure rate, egg reduction, adverse effects	Primary: Both drugs were found to be highly effective against *A lumbricoides* infection, with cure rates >96% and egg reduction rates >99.8%. The efficacy of the two drugs against *T trichiura* infection was low. Mebendazole exhibited a cure rate of 34.7% and egg reduction of 92.3%, as opposed to 13.9% and 63.4%, respectively, for albendazole. More complaints were reported by individuals treated with albendazole than with mebendazole.
Legesse et al.[23] (2004) Albendazole 400 mg as a single dose vs mebendazole 100 mg BID for 3 days	RCT Children ages 6 to 19 years with *Ascaris lumbricoides* and/or *Trichuris trichiura* infections (Ethiopia)	N=534 21 days	Primary: Cure and egg reduction rates	Primary: The cure rate and egg reduction rates obtained with albendazole and mebendazole from the three brands were not significantly different in the treatment of ascariasis. Significant differences were found among the percentage cure and egg reduction rates of the four groups in the treatment of trichuriasis. The highest cure rate (89.8%) and egg reduction rate (99.1%) were observed with Janssen mebendazole (Vermox®), followed by Unibios (India) mebendazole (53.3% cure and 96.5% egg reduction rates), and then East African mebendazole (27.9% cure and 88.5% egg reduction rates) with P<0.05 between the three brands. The lowest cure (17.1%) and egg reduction (69.8%) rates were seen in the albendazole-treated group (P<0.05 compared to the mebendazole brands).
Albanese et al.[26] (2001) Albendazole 400 mg/day for 3 days vs thiabendazole 25-50 mg/kg/day for 2	Case series Patients aged 2 to 60 years with cutanea larva migrans treated with various procedures that were available at the time of diagnosis (Italy)	N=56 Variable duration	Primary: Cure and adverse events	Primary: Thirteen patients received cryotherapy alone, 1 received thiabendazole plus cryotherapy, 6 received thiabendazole, 2 received albendazole plus cryotherapy, and 34 received albendazole alone. A prompt and definitive cure was achieved in all 56 patients, and the therapeutic effectiveness of the various methods used was considered equivalent. Patients receiving cryotherapy complained of pain. Patients treated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days vs cryotherapy vs drug combinations with cryotherapy				thiabendazole experienced nausea, diarrhea, and dizziness. No specific adverse events were reported with albendazole.
Sacko et al.[28] (1999) Albendazole 400 mg as a single dose vs mebendazole 500 mg as a single dose vs pyrantel pamoate 12.5 mg/kg as a single dose vs placebo	PC, RCT, SB Patients aged 3 to 70 years with hookworm infections (Mali, West Africa)	N=145 10 days	Primary: Efficacy (evaluated by 7 procedures which included cure rate)	Primary: Cure rates were reported in 83.8% of patients receiving albendazole, 51.4% of patients receiving mebendazole, 37.8% of patients receiving pyrantel pamoate and 16.7% of patients receiving placebo. Using other efficacy measurements, albendazole was the most effective showing efficacies in the range of 92.1% to 99.5%, depending on the method of evaluation and the particular subset of the treatment group. Neither mebendazole nor pyrantel pamoate was as effective, with efficacies ranging from 60.9% to 89.9%, and 4.8% to 89.7%, respectively.
Tabi et al.[30] (2004) Albendazole 400 mg for 3 days vs	DB, PC, RCT, XO Patients with *Loa loa* microfilaremia (Cameroon)	N=99 1 year	Primary: Microfilarial levels, blood eosinophil counts, packed cell volume (PCV), filarial IgG and IgG4 levels,	Primary: In those initially receiving albendazole (ABZ/PLAC), microfilarial levels decreased significantly by day 90 (P<0.043), but returned to baseline by day 180. In patients receiving albendazole at day 180 (PLAC/ABZ), microfilarial levels also decreased following albendazole (P=0.014). Eleven of 49 patients followed to the end of the study still had parasitemia

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Groups were crossed over at 180 days and followed for an additional 6 months.			tolerance	>20,000 microfilaria/ml. Eosinophil counts remained comparable in both groups except at day 360 when a significant decrease was noted in the PLAC/ABZ group compared to day 1 (P=0.005) and to the ABZ/PLAC group at day 360 (P=0.017). PCV did not vary significantly throughout the study, either within each group or between the two groups. Antifilarial IgG levels did not change significantly for either group. Antifilarial IgG4 levels significantly decreased in the ABZ/PLAC group at day 180 (P=0.022), but by day 360, this difference was no longer significant. There were few posttreatment reactions, the most frequently cited being pruritus (30% and similar in both groups), abdominal discomfort (12%) and urticaria (2%).
Critchley et al.[31] (2005) Albendazole vs placebo, ivermectin, diethylcarbamazine (DEC)	MA Patients with lymphatic filariasis	N=6,997 (7 trials) Up to 2 years	Primary: Microfilariae (mf) prevalence, mf density, antigenemia prevalence or density, adult worms Secondary: Acute filariasis, appearance or disappearance of hydrocele or change in size, adverse events	Primary and Secondary: A comparison of albendazole to placebo detected no effect on mf prevalence after 3-12 months (N=920 participants, 3 trials). One trial (N=499) reported a significantly greater reduction in mf density at 6 months in the albendazole group compared to placebo (34.7% vs 10.3% reduction, respectively, P<0.05). There were no statistically significant differences in the prevalence of circulating filarial antigen positivity from 2 trials after 6-12 months (N=1,090). One trial reported no statistically significant difference in the development of acute filariasis, leg lymphedema, and hydrocele, or improvement of hydrocele and leg lymphedema; however, the trials lacked power so clinically important differences cannot be ruled out. One trial reported no statistically significant difference in systemic adverse events between albendazole and placebo. Another trial reported statistically significant reductions in myalgias and cough for albendazole compared with placebo, but no statistically significant differences in headache, fever or mean treatment impact score. Albendazole performed slightly worse than ivermectin in 2 trials (N=436).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Albendazole was slightly poorer in clearing mf, but this only just reached statistical significance (RR 0.84, 95% CI: 0.72 to 0.98, N=198). There was no statistically significant difference in the number of patients positive for circulating filarial antigen after 12 months for those treated with albendazole or ivermectin. Ivermectin produced higher reductions in mf and antigen densities than albendazole (statistical tests were only applied in one comparison where P=0.02). One trial reported no statistically significant differences in the risk of developing hydrocele, or improvements in lymphedema or hydrocele, but sample sizes were small and confidence intervals wide. There was no statistically significant difference in the number of systemic adverse events between albendazole and ivermectin. When albendazole was added to ivermectin, mf prevalence and density were statistically significantly lower with the combination compared with ivermectin alone in 2 of 3 trials (N=649). There were no significant differences in the remainder of the primary and secondary end points. Compared with DEC, two small trials (N=56) found little difference in mf prevalence over an extended follow-up. One larger trial (N=502) found a statistically significant effect for DEC at 6 months (RR 1.74, 95% CI: 1.05 to 2.88), but not at 3 months. Mf density appeared to fall faster with DEC compared with albendazole; however, there were no statistically significant differences in percentage reductions at any time points. Antigen density was reduced by 17% in the DEC group compared with 3.2% in the albendazole group (P<0.05). The mean score of adverse reaction intensity was lower for albendazole compared with DEC (P<0.05), but the validity and clinical significance of this scoring system was uncertain. There were no significant differences in the remainder of the primary and secondary end points. Two trials compared albendazole plus DEC with DEC alone and found no statistically significant difference in mf prevalence, though one trial favored the combination at 6 months (RR 0.62, 95% CI: 0.32 to 1.21, N=491). This trial also found a significant reduction in mf density with the combination arm vs albendazole (80.4% vs 50.4%, respectively, P<0.05). There were no significant differences in the remainder of the primary and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				secondary end points.
Awadzi et al.[38] (2003) Albendazole 400 mg plus placebo vs ivermectin 200 mcg/kg as a single dose plus placebo vs albendazole 400 mg plus ivermectin 200 mcg/kg as a single dose vs no treatment	DB, PC, RCT Male patients aged 19 to 54 years with moderate to heavy *Onchocerca volvulus* microfiladermia and palpable onchocercal nodules (Ghana)	N=42 1 year	Primary: Viability and reproductive activity of adult worms determined by histopathology and noted by two independent readers, macrofilaricidal efficacy (measured by reductions in mf skin counts), pharmacokinetic parameters, adverse events	Primary: No difference in the viability of the adult worms between the ivermectin groups was reported. The combination was not consistently more effective than ivermectin alone in the effects on reproductive activity. There was no difference between albendazole and no treatment in the effect on adult-worm reproductive activity. There was no difference between the ivermectin groups in the rate at which mf was killed or in the macrofilaricidal efficacy. Both groups reduced mf skin counts by 99% at day 30.The overall reduction of mf skin counts with albendazole was 22% at day 30. There was no significant pharmacokinetic interaction when albendazole was administered with ivermectin. The co-administration of albendazole with ivermectin did not produce more severe adverse effects than ivermectin alone.
Makunde et al.[39] (2004) <u>Co-infections:</u> Albendazole 400 mg and ivermectin 150 mcg/kg as a single dose or placebo; 5 days later the treatment regimen was reversed <u>Single infections:</u>	RCT (Co-infections: DB, PC, XO; single infections: OL) Patients aged 15-55 years co-infected with *Onchocerca volvulus* and *Wuchereria bancrofti* or single infections with *W bancofti* (Tanzania)	N=40 1 year	Primary: Mf intensity, mf prevalence, adverse reactions	Primary: The treatment of co-infections with albendazole and ivermectin resulted in a rapid reduction of mf intensity that was sustained throughout the 12 months of follow-up. Mf prevalence was reduced to 13% and 6% for *O volvulus* and *W bancrofti*, respectively, at 14 days posttreatment but increased throughout the rest of the follow-up ranging from 33%-53% for *O volvulus* and 40%-67% for *W bancrofti*. Treatment of single *W bancrofti* infection with albendazole resulted in a sustained reduction of mf intensity throughout the follow-up period, and the addition of ivermectin significantly improved efficacy at all time points ($P<0.05$). Treatment with albendazole alone resulted in a 15%-38% reduction in mf prevalence, compared to reductions of 73%-100% in the combination group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Albendazole 400 mg and ivermectin 150 mcg/kg as a single dose or albendazole 400 mg as a single dose				There was no significant difference between single and co-infected individuals in the geometric mean mf intensity of *W bancrofti* during albendazole and ivermectin treatment. The frequency of adverse events in co-infected individuals was 63% and 57% in the combination and placebo groups, respectively, and of mild or moderate intensity. The frequency of adverse events in patients with single infections was 50% and 38% in the combination and albendazole monotherapy groups, respectively, and was of similar intensity to those experienced by patients with co-infections. There were no differences in adverse events between treatment groups.
Datry et al.[40] (1994) Albendazole 400 mg/day for 3 days vs ivermectin 150-200 mcg/kg as a single dose	OL, RCT Patients with *Strongyloides stercoralis* of the intestinal tract (France)	N=60 90 days	Primary: Parasitological cure, adverse events	Primary: Ivermectin was significantly more effective in producing parasitological cure than albendazole (83% vs 38%; P<0.01). Clinical and biological adverse reactions were negligible in both treatment groups. The 20 patients who failed therapy were given a second treatment course with ivermectin in a single dose or on two consecutive days. Sixteen patients were cured and the other 4 had only incomplete follow-up.
Dembele et al.[17] (2010) Albendazole 400 mg plus ivermectin 150 mcg/kg administered annually for 2 years (low dose) vs albendazole 800 mg plus ivermectin 400	RCT Patients14 to 65 years of age with *W. bancrofti* microfilariae	N=42 24 months	Primary: Difference in *W. bancrofti* levels at 12 months Secondary: Circulating antigen levels, presence of eosinophilia	Primary: Microfilarial levels were significantly decreased in the high dose group at 12 months (P<0.001), 18 months (P<0.019), and 24 months (P<0.044) compared to standard dose groups. Complete clearance was significantly more common in the high dose group (0 patients with microfilariae at 12, 18 and 24 months) compared to standard dose group (12, 6 and 5 patients with microfilaria at 12, 18 and 24 months, respectively; P<0.001; P=0.02; P=0.02, respectively). Secondary: Circulating antigen levels decreased over 24 months, with differences that were not significant between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg/kg administered bi-annually for 2 years (high dose)				Eosinophilia (>500 cells/mm^3) decreased in both groups, with the most significant change occurring after 6 months.
Knopp et al.[58] (2010) Albendazole 400 mg as a single dose vs albendazole 400 mg plus ivermectin 200 mcg/kg as a single dose vs mebendazole 500 mg as a single dose vs mebendazole 500 mg plus ivermectin 200 mcg/kg as a single dose	PRO, RCT, DB, PC Children in grades 1 through 7 with *T. trichiura* positive stool smears in Tanzania	N=610 Median 29 days	Primary: Cure rate (percentage of children excreting eggs before treatment who became negative), egg reduction rate (ERR) Secondary: Adverse events	Primary: The highest cure rate was 55% in the mebendazole-ivermectin group, followed by a 38% cure rate in the albendazole-ivermectin group. Mebendazole cured significantly more *T. trichiura* compared to albendazole (OR, 2.05; 95% CI, 1.38-3.04). Ivermectin cured significantly more *T. trichiura* compared to placebo (OR 5.4; 95% CI 3.55-8.22). The addition of Ivermectin increased CR from 14 to 47% compared to placebo. The highest ERR was seen in the mebendazole-ivermectin group (97%), which was significantly greater than in the albendazole-ivermectin group (91%). The lowest ERRs were observed in the monotherapy groups. Albendazole treated groups had significantly greater reductions in hookworm infections compared to other groups. Secondary: Abdominal cramps were reported in 13% of children, headache, fatigue and nausea were reported in 5% and 3% experienced diarrhea and vertigo.
Olsen et al.[59] (2009) <u>Albendazole:</u> Albendazole 400 mg as a single dose <u>Mebendazole 1:</u> Mebendazole 100	OL School-age children infected with *Trichuris trichiura*	Albendazole: N=70 14 days Mebendazole 1: N=34 3 days	<u>Albendazole:</u> Primary: Cure and egg reduction rates <u>Mebendazole 1/2:</u> Recovery of adult *T. trichiura* worms	Primary: <u>Albendazole study:</u> At day 7, the cure rate (negative for eggs in stool sample) was 8% and the geometric egg reduction rate was 89% (P<0.001). At day 14, all children were egg-positive and the egg count was 57% higher than baseline (P<0.001). <u>Mebendazole 1 study:</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID for 3 days (study 1) Mebendazole 2: Mebendazole 100 mg BID for 5 days (study 2)		Mebendazole 2: N=35 7 days		With the 3 day course of mebendazole, 4 adult worms were obtained at days 3 to 5 after the start of treatment from two of the 34 children delivering 24 h stool samples. Mebendazole 2 study: With the 5 day course of mebendazole, 10 of 21 infected children expelled a total of 27 worms.
Issaka-Tinorgah et al.[27] (1994) Ivermectin 150 mcg/kg as a single dose vs placebo	PC, RCT, SB Patients over 18 years from a Ghana village highly endemic for guinea worm infections	N=385 15 months	Primary: Emergence and migration of guinea worms, adverse events	Primary: There was no significant difference in the proportion of persons with emergent guinea worms between the 2 treatment groups. Overall, 54 of the 385 participants who were followed for 15 months developed a total of 69 emergent guinea worms. Migration of guinea worms in the tissues was not affected by ivermectin, with 80% of emergent guinea worms located below the knee. There was no difference in the patterns of adverse events between the ivermectin and placebo groups.
Wen et al.[51] (2008) Ivermectin 0.1 mg/kg as a single dose (*Ascaris* infection) vs ivermectin 0.2 mg/kg as a single dose (*Trichuris* or *Enterobius* infection) vs	RCT, DB, MC, PC Fecal egg-positive farmers and children over 6 years of age from rural areas with confirmed intestinal nematode infections	N=816 Single dose	Primary: Cure rates and egg reduction rates Secondary: Adverse events	Primary: The cure rates of ivermectin against *Ascaris* (100%) and *Trichuris* (66.7%) infections were similar to albendazole against *Ascaris* (99.0%; P=1.000) and *Trichuris* (67.7%; P=0.881). Ivermectin was less effective against hookworm (33.3%) and *Enterobius* (52.9%) than albendazole (69.6%; P<0.0001). The percentages of the worms expelled were 41.9%, 48.6%, 9.6%, 0% and 0% in a total of 681worms released on days 1–5 after ivermectin treatment, respectively. The percentages of the worms expelled with albendazole were 0.1%, 24.3%, 52.6%, 22.9% and 0.1% in a total of 744worms released on days 1–5 post-treatment, respectively. Expulsion of worms reached a peak on day 3 after albendazole treatment. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
albendazole 6.7 mg/kg as a single dose				For ivermectin, adverse events included dizziness, abdominal pain and tiredness, which were mild and transient. For albendazole, a total of 2.21% of patients experienced adverse events, including dizziness, vomiting, and diarrhea. No significant difference (P=0.806) between the two treatments in terms of adverse events was shown.
Simonsen et al.[32] (2004) Ivermectin 150-200 mcg/kg vs ivermectin 150-200 mcg/kg and albendazole 400 mg	DB, RCT, Children infected with *Wuchereria bancrofti* (Tanzania)	N=1,829 Duration not specified	Primary: Prevalence and intensities of *W bancrofti* mf and circulating filarial antigen (CFA)	Primary: The overall prevalence of *W bancrofti* mf and CFA was 17.3% and 43.7%, respectively. Both treatment regimens resulted in a considerable decrease in mean mf intensities, with overall reductions being slightly but statistically significantly higher for the combination than for ivermectin alone. The difference in effect between the two regimens was most pronounced at 6 months, whereas it was minor at 12 months after treatment. The relative effect of treatment on mean CFA units was less pronounced than on mf. For both treatment regimens, reductions in CFA intensity appeared to be higher in children who were both CFA and mf positive before treatment, which may suggest that treatment mainly affected the survival and/or production of mf, rather than the survival of adult worms. Adverse reactions were few and mild in both groups, and mainly reported from pretreatment mf and CFA positive children.
Suputtamongkol et al.[15] (2011) Ivermectin 200 mcg/kg as a single dose vs	PRO, RCT, OL Patients ≥18 years of age with *S. stercoralis* larvae on microscopy (chronic strongyloidiasis)	N=90 19 to 36 weeks	Primary: Cure (clinical improvement and absence of larvae in stool at day 14 of treatment and through follow up), failure (presence of larvae 2 weeks	Primary: Parasite elimination occurred in 63.3% of albendazole patients, in 96.8% of patients receiving a single dose of ivermectin, and in 93.1% of patients receiving two doses of ivermectin (P=0.006). Patients receiving albendazole had 14.7 times (95% CI, 1.8-111.9) and 5.7 times (95% CI, 1.3-25.7) higher risk for reinfection/relapse of strongyloidiasis compared to patients receiving single-dose or double-dose ivermectin therapy, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ivermectin 200 mg/kg as a single dose given 2 weeks apart vs albendazole 400mg BID for 7 days			after initiation of treatment or reappearance of larvae during follow-up)	Overall, albendazole and ivermectin were well tolerated.
Bregani et al.[33] (2006) Ivermectin 200 mcg/kg biweekly for 3 subsequent administrations vs diethylcarbamazine (DEC) 200 mg BID for 21 days, course repeated if full response not achieved vs mebendazole 100 mg BID for 28 days vs praziquantel 40 mg/kg as a single dose	OL Patients aged 9 to 90 years with *Mansonella perstans* infections (Chad)	N=165 15 months	Primary: Mf density, median eosinophil percentage (MEP), recovery (full recovery defined as the number of patients with complete clearance of blood microfilaria and partial recovery defined as number of patients with reduction of blood microfilaria without complete clearance), adverse events	Primary: In the DEC group, mf density significantly decreased (P<0.01), while MEP increased both after the first (P<0.01) and second course of treatment (P=NS). However, the second course of treatment further improved the full recovery (complete elimination of mf) from 3.8% to 15%. In the mebendazole group, a significant decrease in mf was observed (P<0.01), while MEP did not change (P=NS). A full recovery and overall response were observed in 21.7% and 87.0% of patients, respectively. In the thiabendazole group, a statistically significant decrease in mf was reached only after the second therapeutic step (-33.3%; P<0.04). Full response was achieved in one case (6.7% of patients), and an overall response of 73% was observed in the group who received two consecutive treatments. Thiabendazole was significantly less effective both on mf reduction and on full response than DEC and mebendazole. In the DEC plus mebendazole treatment group, a highly significant fall in mf was seen (P<0.01), while MEP values showed the same trend towards an increase as in the DEC group. No significant difference was observed in mf reduction among the three treatment regimens using the combination of DEC and mebendazole. The combination of DEC and mebendazole produced full and overall recovery rates of 37% and 96%, respectively. There were no significant changes in mf density in the groups receiving ivermectin, praziquantel or no treatment. Full and overall recovery were reported in 0% and 44.4% of patients, respectively, who received no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs thiabendazole 50 mg/kg for children or 3 g for adults as a single dose or in double administration on the first and eighth days vs diethylcarbamazine 200 mg BID for 21 days plus mebendazole 100 mg for 21 days or 100 mg BID for 14 or 21 days				treatment. All treatments were well tolerated and no adverse effects were observed.
Fobi et al.[34] (2005) Gardon et al.[35] (2002) Kamgno et al.[36] (2004) Ivermectin 150 mcg/kg annually (reference group) vs ivermectin 150 mcg/kg every 3 months	DB, RCT Men aged 18-60 years with *Onchocerca volvulus* infections (Cameroon)	N=657 3 years	Primary: Vital status of female worms[35], adverse events[36], ophthalmological exam[34], ocular and visual symptoms[34] Secondary [35]: Fertility of female worms, skin mf, number of non-fertile female and male worms	Primary and Secondary: After 3 years, more female worms had died in the groups treated every 3 months than in the reference group (OR 1.84 [95% CI: 1.23 to 2.75], P=0.003 for 150 mcg/kg; and 2.17 [95% CI: 1.42 to 3.31], P<0.001 for the 400-800 mcg/kg dose). Female worms were also less fertile in these groups than in the reference group (0.24 [95% CI: 0.14 to 0.43], P<0.0001; and 0.14 [95% CI: 0.06 to 0.29], P<0.0001, respectively). No difference was recorded between groups treated yearly (P=0.83 for the proportion of dead females). More than 90% of patients on yearly treatment had mf in their skin snips (difference 1.9% [95% CI: 3.9 to 7.8], P=0.52), compared with 40% and 26%, respectively, in the groups treated every 3 months at 150 mcg/kg and at high doses (difference 13.8% [95% CI: 2.5 to 25.1], P=0.0180). The mean numbers of skin mf did not differ between the two groups treated yearly (P=0.45).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ivermectin 400 mcg/kg then 800 mcg/kg annually vs ivermectin 400 then 800 mcg/kg every 3 months Every patient was given a clearing dose of 150 mcg/kg ivermectin prior to the start of the study.				High doses (400-800 mcg/kg) administered annually produced little marginal parasitological benefit compared to 150 mcg/kg. After the first dose, dosing every 3 months was associated with a reduced risk of reactions, especially edematous swellings, pruritus and back pain. Edematous swellings and subjective ocular troubles were found to be associated with high doses of ivermectin. Transitory subjective visual problems were reported more frequently in the two groups receiving the high ivermectin doses than in the reference group (P<0.03 and P<0.001 for the ivermectin 800 mcg/kg annual and every 3-month regimens, respectively). In the ophthalmological examinations, the only differences recorded between the groups were a lower prevalence and mean number of microfilariae in the anterior chamber in the groups treated every 3 months, and, at the first examination round, a higher prevalence of early lesions of the iris in the group treated at high doses annually. Results of the ophthalmological exam did not show the cause of the transitory ocular complaints, nor explain why they were more frequent in the groups treated with higher doses.
Awadzi et al.[37] (1999) Ivermectin 150 mcg/kg as a single dose vs ivermectin 150 mcg/kg or placebo, then 400 mcg/kg vs ivermectin 150 mcg/kg or placebo,	DB, PC, RCT Males infected with *Onchocerca volvulus* (Ghana)	N=100 21 months	Primary: Nodule characteristics, adult worm viability, reproductive activity, skin and ocular mf	Primary: There were no significant trends among the dosage regimens regarding the number of live worms per nodule, the male: female ratio or in the number of nodules with live mf (P>0.05). There was however a significant trend to a reduction in the number of nodules without male worms with increasing doses of ivermectin (P=0.02). There was no significant trend in mortality among female and male worms in the treated groups (P>0.05). Increasing doses of ivermectin had no marked effect on embryogenesis. There was a significant trend towards an increase in the number of female worms with nearly empty uteri (P=0.04), and a reduction in the proportion of female worms with young embryos (P=0.015) and coiled mf (P=0.004) with increasing doses. There was no significant trend with dose in the proportion of worms with young oocytes only, with stretched mf, or with degenerate stretched mf. Between 95% and 100% of live male worms contained intact spermatozoa with no differences between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
then 600 mcg/kg vs ivermectin 150 mcg/kg or placebo, then 800 mcg/kg vs ivermectin 800 mcg/kg for 2 doses				At days 30 and 180, the higher dose groups had a greater suppression of skin mf (P<0.05) but the effect was minor (maximum differences were 1.6%) and transient. By 1 year, the mean skin mf densities were again similar in all groups. The clearance of ocular mf was also similar in all groups. There was no significant difference in ocular mf between the treatment groups. Overall, the treatment groups maintained at 1 year a 96% reduction on initial counts for both skin and ocular mf. Total doses of ivermectin (≤1,600 mcg/kg) were not more effective than 150 mcg/kg. They did not reproduce the marked inhibitory effects of the repeat standard-dose regimens on embryogenesis, or the modest effect on adult worm viability, at comparable total doses.
Tarr et al.[41] (2003) Ivermectin rectal enema 200 mcg/kg/day for 7 days (prepared from tablets) in combination with nasogastric albendazole and ivermectin for 14 days, an additional 5 days of oral ivermectin were given 2 weeks after hospital discharge	Case report 55-year-old female renal transplant recipient with *Strongyloides stercoralis* hyperinfection syndrome and progressive ileus unresponsive to nasogastric albendazole and ivermectin	N=1 19 months	Primary: Clinical symptoms, presence of larvae, adverse events	Primary: The patient improved markedly within approximately 72 hours and recovered fully. Stool studies, done periodically and, in the absence of symptoms, were negative for *S stercoralis.* The ivermectin enemas were well tolerated, diarrhea was not induced. Nausea, abdominal pain, and shortness of breath resolved, and oxygen requirements as well as amounts of larvae in nasogastric aspirate samples decreased. At 19 months, the patient had no gastrointestinal symptoms.
Albonico et al.[24] (2003) Mebendazole 500 mg vs	PC, RCT Children with *Ascaris lumbricoides*, hookworm and/or *Trichuris trichiura* infections (Pemba	N=904 21 days	Primary: Egg counts, cure rates, reductions in prevalence and egg reduction rates	Primary: Follow-up egg counts, cure rates, reductions in prevalence and egg reduction rates for the three nematode infections were statistically significantly better with all of the drug regimens compared with those of baseline, except for cure rates for hookworm infections with mebendazole and for *T trichiura* infections with levamisole (although in both cases the mean egg counts were reduced substantially). Compared with placebo, all drug treatments produced significantly higher cure rates and egg reduction

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
levamisole 40 mg or 80 mg vs mebendazole 500 mg plus levamisole 40 mg vs placebo	Island, Zanzibar)			rates, and lower prevalence at follow-up, except for the egg reduction rate for levamisole in *T trichiura* infections. Both drugs had very high efficacy (98.5% and 99.1% egg reduction rates for levamisole and mebendazole, respectively) against *A lumbricoides*. Mebendazole alone and in combination with levamisole had better efficacy than levamisole alone for *T trichiura* infection (81% and 85% vs 41.5% egg reduction rates, P<0.001). Levamisole treatment produced a marginally significant reduction in prevalence of hookworm infection, which was greater than the reduction seen with mebendazole (8.9% vs 3.6%, P<0.05); the combination had better efficacy in reducing prevalence than either drug alone (23.6%, P<0.001). The egg reduction rate for hookworm infection was 88.7% for the combined treatment, but significantly less for either drug alone (61.3% for levamisole and 52.1% for mebendazole, P<0.001). No difference in mebendazole efficacy was found in children who had been treated repeatedly compared with those who had not been treated previously.
Albonico et al.[25] (2002) Mebendazole 500 mg as a single dose vs pyrantel-oxantel* 10 mg/kg as a single dose (one tablet contained 150 mg of each drug) vs placebo	DB, PC, RCT Children ages 6 to 9 years with *Ascaris lumbricoides*, hookworm and/or *Trichuris trichiura* infections (Pemba Island, Zanzibar)	N=1,329 21 days	Primary: Cure and egg reduction rates Secondary: Adverse events	Primary: Both mebendazole and pyrantel-oxantel were very effective in eliminating *A lumbricoides* infection, inducing cure rates of more than 96% and reducing the mean egg counts by more than 95% (P<0.001 compared to 27.9% and 9.8%, respectively, for placebo). Both drugs had moderate efficacy against *T trichiura* infection, but pyrantel-oxantel had a higher cure rate (38.25% vs 25.2%, P<0.01), though the reductions in egg counts did not differ significantly and were more than 80% for both drugs. Mebendazole and pyrantel-oxantel had similar, poor efficacy in curing hookworm infections (13.2% and 12.7%, respectively), and had a moderate effect in reducing the egg counts (68% and 67%, respectively). However, both drugs produced higher cure rates than placebo (6.2%, P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No adverse events were reported after any of the treatments.
Cleary et al.[52] (2007) Mebendazole 100 mg as a single treatment every 3 months vs mebendazole 100 mg as a single treatment every 12 months	CC Persons living along Amazon tributaries in Northeastern Peru	N=126 (stool samples) 2 years	Primary: Cure rates	Primary: At 12 months and 24 months, 91.0% and 92.5% of the treatment group, respectively, had negative stool samples for *A. lumbricoides*. Changes in growth were evaluated based upon the quantity of individuals who were less than the 3rd percentile value for weight. A 12% improvement in those subjects below the 3rd percentile was observed over the villagers living in remote locations (control villages).
Flohr et al.[53] (2007) Study 1 Mebendazole 500 mg once vs placebo Study 2 Mebendazole 500 mg daily for 3 days vs albendazole 400 mg once vs	RCT Study 1 6- to 11-year-old children attending school in Khanh Hoa province, central Vietnam Study 2 Adults aged 16 and older living in one village in Khanh Hoa province, central Vietnam	N=271 (Study 1) N=209 (Study 2) 2 weeks	Primary: Hookworm intensity as measured by percent decline in arithmetic mean eggs per gram after treatment Secondary: Cure from hookworm infection	Primary: Study 1 Efficacy in terms of percentage reduction in arithmetic mean eggs per gram feces relative to placebo was not significantly different between the mebendazole treatment group and the placebo group (31%, 95% CI −9 to 56%). Study 2 The estimated reduction in arithmetic mean eggs per gram of feces relative to placebo was 63% (95% CI 30–81%), 75% (95% CI 47– 88%), and 88% (95% CI 58–97%) for triple dose mebendazole, single dose albendazole, and triple dose albendazole, respectively. Secondary: Study 1 There was no significant difference between treatments in the proportion of infected children cured at 2 weeks: 33% in the placebo group and 38% in the mebendazole group. Study 2 The cure rates were 26% for three dose mebendazole, 45% for single dose albendazole, 79% for three dose albendazole, and 35% for placebo. Only

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
albendazole 400 mg daily for 3 days vs placebo				the triple dose albendazole course was significantly superior to placebo in terms of cure (P<0.001).
De Clercq et al.[29] (1997) Mebendazole 500 mg as a single dose vs pyrantel pamoate 10 mg/kg as a single dose vs placebo vs no treatment	PC, RCT, SB Patients aged 3 to 71 years with hookworm infections (Mali, West Africa)	N=103 4 weeks	Primary: Cure rate and fecal egg counts	Primary: Patients treated with pyrantel pamoate experienced the highest cure rates (44.8%), followed by no treatment (25%), mebendazole (22.9%) and placebo (22.6%). Patients treated with pyrantel pamoate experienced the greatest reduction in egg counts (-75%), followed by no treatment (-39.5%), placebo (-32.7%) and mebendazole (+6.5%). Male subjects carried significantly more intense infections compared with females, but there was no gender difference in response to treatment.
Trematodes (Flukes)				
Kjetland et al.[42] (2006) Praziquantel 40 mg/kg as a single dose or 60 mg/kg in two divided doses (5 hours apart)	OL Women aged 20 to 49 years infected with *Schistosoma haematobium* (Zimbabwe)	N=527 12 months	Primary: Cure rate, ova, change in shape and size of lesions, detection of sexually transmitted diseases (STDs)	Primary: *S haematobium* ova were found in 39% of women at baseline, which decreased to 7% and 5% at 3 and 12 months, respectively. At baseline, 46% of the women had “sandy patches” (areas of granulomatous lesions containing schistosome ova), 44% had neovascularization, and 23% had contact bleeding. Although urinary ova excretion decreased following treatment (OR 10.3, 95% CI: 3.8 to 27.8, P<0.001), praziquantel treatment was not associated with a significant reduction in genital lesions or contact bleeding (P=0.31

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				to P=0.94). There was no influence of human immunodeficiency virus (HIV) seropositivity on the effect of treatment. There was no significant association between the STDs and sandy patches, neovascularization or contact bleeding.
Li et al.[43] (2002) Praziquantel 40 mg/kg given at least 3 times over a 5-year period	OL Patients aged 9 to 65 years infected with *Schistosoma japonicum* were selected for the 5-year longitudinal study, all egg-positive subjects were cured at the start of the study with praziquantel (China)	N=120 5 years	Primary: Prevalence, intensity of infection (defined as geometric mean eggs per gram), ultrasound changes	Primary: Prevalence of schistosome infection fell by 43% and intensity of infection declined by 80% over the 5-year study. However, transmission persisted at 13% per year for re-infection or new infection in the cohort. The prevalence of left-lobe enlargement and dilated portal vein fell significantly (P<0.01) to about half, although a few patients progressed during the study. At study endpoint, infection was nearly twice as common if the portal vein was dilated (23% vs 13%, respectively), but this association was not statistically significant (P>0.05). However, end point infection was even more strongly associated with left-lobe enlargement (57% vs 15%, P<0.01). The proportions of subjects with improved parenchymal and periportal fibrosis were much higher than the proportions of subjects that progressed (P<0.05). Reduction of prevalence and intensity of infection and improvement of subclinical morbidity were benefits of repeated treatments.
Kabatereine et al.[44] (2003) Praziquantel 40 mg/kg as a single dose, repeated 6 weeks later	OL Patients aged 5 to 54 years infected with *Schistosoma mansoni* (Uganda)	N=482 12 weeks	Primary: Cure rate, reduction in intensity of infection, adverse reactions	Primary: The cure rate following the first and second treatments was 41.9% and 69.1%, respectively. The cure rate was higher in adults than in children, irrespective of intensity of infection. In addition, the cure rate declined markedly with increasing intensity of infection. The reduction in intensity of infection was marked, being 97.7% and 99.6% after the first and second treatments, respectively. A pre- and post-treatment symptom questionnaire revealed a broad range of side effects, including abdominal pain and diarrhea. However, no serious or long-lasting complications affecting compliance were observed.
Raso et al.[45] (2004)	OL	N=200	Primary: Cure rate, egg	Primary: The overall cure rate, assessed 6 weeks posttreatment, was 60.9%. The

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Praziquantel 40 mg/kg as a single dose	Patients aged 5 days to 91 years infected with *Schistosoma mansoni* (Côte d'Ivoire)	6 weeks	reduction rate, adverse reaction	overall cure rates among individuals who had light, moderate or heavy infections pretreatment were 70.3%, 50.0% and 33.3%, respectively. The total egg count reduction was 61.4%. Among the 200 treated patients, 25 (12.5%) reported 1 or more side effects within 24 hours posttreatment. The most frequent side effects were abdominal pain, dizziness and diarrhea.
Picquet et al.[46] (1998) Praziquantel 40 mg/kg as a single dose repeated in 40 days	OL Adults and children infected with *Schistosoma mansoni* (Senegal)	N=113 153 days	Primary: Cure rate, egg counts, intensity reduction rate	Primary: The overall cure rate after the first treatment was 42.5% and was 76.1% after the second treatment. The greatest increase in cure rate between the 2 treatments was in those individuals who were initially the most heavily infected (>1,000 eggs/gram of feces). The overall intensity reduction rate after the first and second treatments were 70.7% and 88.1%, respectively. There was no apparent difference in cure rate between younger (<20 years) and older individuals (>20 years). There was no evidence for the existence of a praziquantel tolerant strain of *S mansoni*.
Degu et al.[47] (2002) Praziquantel 40 mg/kg as a single dose	OL All children aged 10 to 14 years old attending the primary school in Gorgora, Amhara (Ethiopia)	N=325 6 weeks	Primary: Prevalence of *Schistosoma mansoni*, fecal eggs, egg reduction rate, evidence of resistance	Primary: Of the 325 children examined, 50.8% had *S mansoni* eggs in the first fecal sample. Six weeks after treatment, 94% of the children had no detectable *S mansoni* eggs, and the average egg reduction rate was 97%. Sixty-seven of the children reported that they had previously been diagnosed with schistosomiasis and had been treated with praziquantel. Of these, 32 (47.8%) were found to be excreting eggs, a proportion not significantly different from the prevalence among children who did not report previous infection (52.2%). No evidence of praziquantel resistance was detected.
Hou et al.[54] (2008) Praziquantel 60	RCT, DB, PC Patients aged 10–60 years weighing over	N=205 45 days	Primary: Human infection status.	Primary: All groups had similarly high treatment efficacies ranging from 95.7% (group D) to 98% (group A). Comparisons of group A with group B and group C with group D for the determination of the additive effect of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg plus 6 mg/kg artemether (group A) vs praziquantel 60 mg/kg (group B) vs praziquantel 120 mg/kg plus 6 mg/kg artemether (group C) vs praziquantel 120 mg/kg (group D)	25 kg and diagnosed with acute schistosomiasis japonica		Secondary: Hemoglobin and alanine aminotransferase (ALT) levels over time	artemether showed that there were no significant difference in treatment efficacies in the regimens that included artemether (P=0.947). The two different dosages of praziquantel provided the same level of efficacy. Fever subsided in 3.9, 5.1, 6.4 and 5.2 days post-artemether treatment in groups A, B, C and D, respectively (P=0.027). Combined artemether and praziquantel (60 mg/kg) treatment was the most effective for fever clearance. Patients in groups A to D remained in hospital on average 6.4, 8.0, 9.4 and 8.9 days, respectively; the hospital stay of patients in group A was significantly shorter than in the other groups (P=0.023). Secondary: Little change in hemoglobin levels of patients was observed over the course of the trial and there were no significant differences between the groups both pre- and post-treatment. In total, 34 cases had an elevated ALT level before treatment, of which 24 returned to normal at day 20 post-artemether treatment. There were no statistically significant differences between the groups, and the mean levels of ALT at 20 days post-artemether treatment dropped to normal levels.
Martins-Leite et al.[55] (2008) Praziquantel 50 mg/kg once and repeated after 2 months if necessary	OL Patients presenting with an infection with *S. mansoni* (Brazil)	N=91 1 year	Primary: Immune response and reversal of Symmers' fibrosis	Primary: A significant reduction in the mean values for longitudinal and anteroposterior measurements of liver (left and right lobes), as well as the diameters of portal and splenic veins was observed. In contrast, the spleen measurements were augmented significantly. The numbers of individuals with non-detectable fibrosis and those with incipient fibrosis increased. One year after treatment with praziquantel, 29% of individuals reverted to a lower degree of fibrosis, 4% experienced an increase in fibrosis, and 67% did not experience any change. The proportion of individuals with pathology (grade 2 or 3) decreased from 24% prior to treatment to 4% after treatment (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Nine (9.9%) participants remained positive for the presence of eggs of *S. mansoni*, and their infection levels ranged from 4 to 184 eggs/g. When distributed according to the degree of hepatic fibrosis (classified into three groups as determined by posttreatment ultrasound measurements), no statistically significant differences in levels of cytokines could be detected. However, when the levels of these cytokines were categorized as low or high (on the basis of the median value of each cytokine titer for 91 patients) for individuals not presenting (group 0) or presenting (groups 1 and 2) with fibrosis, the proportion of subjects with a high level of IL-13 was significantly larger in the latter two groups.
Koukounari et al.[56] (2007) Praziquantel and albendazole Large-scale administration of the agents against soil-transmitted helminths by the national Burkinabe´ helminth control program.	EPI Burkinabe´ children 6–14 years old	N=1,727 12 months	Primary: Parasitological and morbidity data	Primary: During the 12 months between examinations, the overall prevalences of *S. haematobium, S. mansoni,* and hookworm infections decreased significantly (P<0.001). For both years examined, *Ascaris lumbricoides* infection was absent, and the prevalence of *Trichuris trichiura* infection was estimated to be 1.1% at baseline and totally absent 1 year later. A significant increase in mean Hb concentration (P<0.001) and a significant decrease in the prevalence of anemia (P=0.021) were also observed. The unadjusted observed changes in both recent and chronic undernutrition from baseline to follow-up were not significant (P=0.135 and P=0.093, respectively).
Miscellaneous Infections				
Namwanje et al.[57] (2011) <u>SCH Alone:</u> ALB+IVM+PZQ vs	RCT Children 5-18 years of age with lymphatic filariasis (LF) alone; schistosomiasis (SCH) alone; soil-	N=235 5 weeks	Primary: Adverse drug events (ADRs) with triple therapy Secondary: Efficacy (mean percentage	Primary: There were no significant differences in ADRs in the treatment group compared to the control group. A total of 22.2% of the test group (triple therapy) reported an ADR compared to 66.7% of the control group. The most frequent ADRs reported were abdominal pain and headache. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PZQ STH Alone: ALB+IVM+PZQ vs ALB LF Alone: ALB+IVM+PZQ vs ALB +IVM LF+SCH: ALB+IVM+PZQ vs ALB+IVM followed by PZQ after 1 week LF+SCH+STH: ALB+IVM+PZQ vs ALB+IVM followed by PZQ after 1 week ALB: Albendazole 400 mg as a single dose; IVM:	transmitted helminthiasis (STH) alone; LF+SCH and LF+SCH+STH		reduction in egg counts)	The overall mean reduction in SCH eggs for the test group and control group was 99%. There was no significant difference among the treatment groups. The overall mean reduction in STH eggs for the test group was 94% and 93% for control group. There was no significant difference among the treatment groups. The overall mean reduction in LF microfilariae was 92% in the test group and 99% in the control group. There was no significant difference among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ivermectin 200 mcg/kg as a single dose; PZQ: Praziquantel 40 mg/kg as a single dose				

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: CC=case control, CI=confidence interval, DB=double-blind, EPI=epidemiologic study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PRO=prospective, OD=odds ratio, RCT=randomized-controlled trial, RR=relative risk, XO=crossover

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Anthelmintics

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Albendazole	tablet	Albenza®	$$$	N/A
Ivermectin	tablet	Stromectol®	$$	N/A
Mebendazole	chewable tablet	N/A	N/A	$
Praziquantel	tablet	Biltricide®	$$$	N/A
Pyrantel pamoate	suspension‡	Reese Pinworm®	$	N/A

‡Product is available over-the-counter.
N/A=Not available

X. Conclusions

The anthelmintics are approved for the treatment of cestode, nematode and trematode infections.[1-6] Infections caused by helminths, or parasitic worms, are among the most prevalent infections in the world and are a leading cause of morbidity.[7] Pinworm infections (*Enterobiasis vermicularis*) are the most common helminthic infections in the U.S., followed by *Ascaris lumbricoides*.[9] Mebendazole is available in a generic formulation and pyrantel pamoate is available over-the-counter.

Albendazole is approved for the treatment of cestode infections, including cystic hydatid disease (liver, lung, and peritoneum) and parenchymal neurocysticercosis. Guidelines recommend albendazole as initial therapy and clinical trials have demonstrated successful treatment of cystic hydatid disease and parenchymal neurocysticercosis with this agent.[11-12,14,16,18-19,48,50] Although albendazole has limited FDA-approved indications,

this agent is also recommended as initial therapy for the treatment of ascariasis, hookworms, pinworms and whipworms.[11-12] Clinical studies have demonstrated comparable efficacy with albendazole and mebendazole for the treatment of ascariasis.[22-23] Three studies demonstrated that albendazole was more effective than mebendazole for treating hookworm infections, while three other studies found that mebendazole was more effective than albendazole for treating whipworm.[21-23,28,53,58]

Ivermectin is approved for the treatment of nematode infections, including onchocerciasis and strongyloidiasis of the intestinal tract. Guidelines recommend ivermectin as initial therapy and clinical trials have demonstrated successful treatment of onchocerciasis and strongyloidiasis with this agent.[11-12,35,37-38,40]

Mebendazole is approved for the treatment of nematode infections, including ascariasis, hookworms, pinworms, and whipworms. Guidelines recommend mebendazole or albendazole as initial therapy for the treatment of these infections.[11-12] Clinical trials have demonstrated successful treatment of helminthic infections with mebendazole.[21-25,28,52,58]

Praziquantel is approved for the treatment of trematode infections, including clonorchiasis, opisthorchiasis and schistosomiasis. Guidelines recommend praziquantel as the primary treatment for these infections.[11-12] Several clinical trials have demonstrated successful treatment of schistosomiasis with praziquantel.[42-47,54-56]

Pyrantel pamoate is only approved for the treatment of pinworms. It is considered either a primary treatment, or an alternative treatment option, depending on the guideline.[11-12]

Albendazole, ivermectin, and praziquantel are considered first-line therapy for some parasitic diseases that are not commonly seen in the U.S. Therefore, patients with a diagnosis of one of these uncommon helminthic infections should be allowed approval for a brand anthelmintic through the medical justification portion of the prior authorization process.

Therefore, all brand anthelmintics within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand anthelmintic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2010. Available from Wolters Kluwer Health, Inc. Accessed September 2011.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2010; September 2011.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed September 2011.
4. Albenza® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; October 2009.
5. Stromectol® [package insert]. Whitehouse Station, NH: Merck & Co., Inc.; May 2010.
6. Biltricide® [package insert]. Whitehouse Station, NH: Merck & Co., Inc.; August 2010.
7. Maguire JH. Introduction to Helminth Infections. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 6th ed. Philadelphia: Elsevier Inc.; 2005.
8. Loukas A, Hotez P. Chemotherapy of Helminth Infections. In: Brunton LL, ed. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. New York: McGraw-Hill; 2006.
9. Maguire JH. Intestinal Nematodes (Roundworms). In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 6th ed. Philadelphia: Elsevier Inc.; 2005:3260-7.
10. Anandan JV. Parasitic Diseases. In: Dipiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiological Approach. 6th ed. New York: McGraw-Hill; 2005:2067-80.
11. Chambers, H.F., et al. (Eds.), Antiparasitic Therapy, Sanford Guide–Web Edition. Available at: http://webedition.sanfordguide.com. Accessed December 2011.
12. American Academy of Pediatrics. In: Pickering LK, ed. Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009. Available at: http://aapredbook.aappublications.org/cgi/content/full/2009/1/3.131. Accessed November 2011.
13. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among Hematopoietic Cell Transplantation Recipients: A Global Perspective. Biol Blood Marrow Transplant 2009;15:1143-1238.
14. Kaur S, Singhi P, Singhi S, et al. Combination therapy with albendazole and praziquantel versus albendazole alone in children with seizures and single lesion neurocysticercosis: a randomized, placebo-controlled double blind trial. Pediatr Infect Dis J 2009;28:403-6.
15. Suputtamongkol Y, Premasathian N, Bhumimuang K, et al. Efficacy and safety of single and double doses of ivermectin versus 7-day high dose albendazole for chronic strongyloidiasis. PLoS Negl Trop Dis 2011;5:e1044.
16. Chaurasia RN, Garg RK, Agarwall A, et al. Three day albendazole therapy in patients with a solitary cysticercus granuloma: a randomized double blind placebo controlled study. Southeast Asian J Trop Med Public Health 2010;41:517-25.
17. Dembele B, Coulibaly YI, Dolo H, et al. Use of high-dose, twice-yearly albendazole and ivermectin to suppress Wuchereria bancrofti microfilarial levels. Clin Infect Dis 2010;51:1229-35.
18. Wen H, Zou P, Yang W, et al. Albendazole chemotherapy for human cystic and alveolar echinococcosis in north-western China. Trans R Soc Trop Med Hyg. 1994;88:340-3.
19. Del Brutto OH, Roos KL, Coffey CS, Garcia HH. Meta-analysis: cysticidal drugs for neurocysticercosis: albendazole and praziquantel. Ann Int Med. 2006 Jul 4;145(1):43-51.
20. Belizario VY, Amarillo ME, de Leon WU, et al. A comparison of the efficacy of single doses of albendazole, ivermectin, and diethylcarbamazine alone or in combinations against *Ascaris* and *Trichuris* species. Bull World Health Organ. 2003;81(1):35-42.
21. Muchiri EM, Thiong'o FW, Magnussen P, Ouma JH. A comparative study of different albendazole and mebendazole regimens for the treatment of intestinal infections in school children of Usigu Division, Western Kenya. J Parasitol. 2001 Apr;87(2):413-8.
22. Legesse M, Erko B, Medhin G. Efficacy of albendazole and mebendazole in the treatment of *Ascaris* and *Trichuris* infections. Ethiop Med J. 2002 Oct;40(4):335-43.
23. Legesse M, Erko B, Medhin G. Comparative efficacy of albendazole and three brands of mebendazole in the treatment of ascariasis and trichuriasis. East Afr Med J. 2004;81(3):134-8.
24. Albonico M, Bickle Q, Ramsan M, et al. Efficacy of mebendazole and levamisole alone or in combination against intestinal nematode infections after repeated targeted mebendazole treatment in Zansibar. Bull World Health Org. 2003;81(5):343-52.

25. Albonico M, Bickle Q, Haji HJ, et al. Evaluation of the efficacy of pyrantel-oxantel for the treatment of soil-transmitted nematode infections. Trans R Soc Trop Med Hyg. 2002;96:685-90.
26. Albanese G, Venturi C, Galbiati G. Treatment of larva migrans cutanea (creeping eruption): a comparison between albendazole and traditional therapy. Int J Dermatol. 2001;40:67-71.
27. Issaka-Tinorgah A, Magnussen P, Bloch P, Yakubu A. Lack of effect of ivermectin on prepatent guinea-worm: a single-blind, placebo-controlled trial. Trans R Soc Trop Med Hyg. 1994;88:346-8.
28. Sacko M, De Clercq D, Behnke JM, et al. Comparison of the efficacy of mebendazole, albendazole and pyrantel in treatment of human hookworm infections in the southern region of Mali, West Africa. Trans R Soc Trop Med Hyg. 1999;93:195-203.
29. De Clercq D, Sacko M, Behnke J, et al. Failure of mebendazole in treatment of human hookworm infections in the southern region of Mali. Am J Trop Hyg. 1997;57(1):25-30.
30. Tabi TE, Befidi-Mengue R, Nutman TB, et al. Human loiasis in a Cameroonian village: a double-blind, placebo-controlled, crossover clinical trial of a three-day albendazole regimen. Am J Trop Med Hyg. 2004;71(2):211-5.
31. Critchley J, Addiss D, Gamble C, et al; International Filariasis Review Group. Albendazole for lymphatic filariasis. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD003753.
32. Simonsen PE, Magesa SM, Dunyo SK, et al. The effect of single dose ivermectin alone or in combination with albendazole on *Wuchereria bancrofti* infection in primary school children in Tanzania. Trans R Soc Trop Med Hyg. 2004;98(8):462-72.
33. Bregani ER, Rovellini A, Mbaidoum N, Magnini MG. Comparison of different anthelminthic drug regimens against *Mansonella perstans* filariasis. Trans R Soc Trop Med Hyg. 2006;100:458-63.
34. Fobi G, Gardon J, Kamgno J, et al. A randomized, double-blind, controlled trial of the effects of ivermectin at normal and high doses, given annually or three-monthly, against *Onchocerca volvulus*: ophthalmological results. Trans R Soc Trop Med Hyg. 2005;99:279-89.
35. Gardon J, Boussinesq M, Kamgno J, et al. Effects of standard and high doses of ivermectin on adult worms of *Onchocerca volvulus*: a randomized controlled trial. Lancet. 2002 Jul 20;360:203-10.
36. Kamgno J, Gardon J, Gardon-Wendel N, et al. Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. Trans R Soc Trop Med Hyg. 2004;98:496-504.
37. Awadzi K, Attah SK, Addy ET, Opoku NO, Quartey BT. The effects of high-dose ivermectin regimens on *Onchocerca volvulus* in onchocerciasis patients. Trans R Soc Trop Med Hyg. 1999;93:189-94.
38. Awadzi K, Edwards G, Duke BOL, et al. The co-administration of ivermectin and albendazole—safety, pharmacokinetics and efficacy against *Onchocerca volvulus*. Ann Trop Med Parasitol. 2003;97(2):165-78.
39. Makunde WH, Kamugisha LM, Massaga JJ, et al. Treatment of co-infection with bancroftian filariasis and onchocerciasis: a safety and efficacy study of albendazole with ivermectin compared to treatment of single infection with bancroftian filariasis. Filaria J. 2003 Nov 6;2(1):15.
40. Datry A, Hilmarsdottir I, Mayorga-Sagastume R, et al. Treatment of *Strongyloides stercoralis* infection with ivermectin compared with albendazole: results of an open study of 60 cases. Trans R Soc Trop Med Hyg. 1994;88(3):344-5.
41. Tarr PE, Miele PS, Peregoy KS, et al. Case report: rectal administration of ivermectin to a patient with *Strongyloides* hyperinfection syndrome. Am J Trop Med Hyg. 2003 Apr;68(4):453-5.
42. Kjetland EF, Mduluza T, Ndhlovu PD, et al. Genital schistosomiasis in women: a clinical 12-month in vivo study following treatment with praziquantel. Trans R Soc Trop Med Hyg. 2006;100:740-52.
43. Li YS, Sleigh AC, Li Y, et al. Five-year impact of repeated praziquantel treatment on subclinical morbidity due to *Schistosoma japonicum* in China. Trans R Soc Trop Med Hyg 2002:96:438-43.
44. Kabatereine NB, Kemijumbi J, Ouma JH, et al. Efficacy and side effects of praziquantel treatment in a highly endemic *Schistosoma mansoni* focus at Lake Albert, Uganda. Trans R Soc Trop Med Hyg. 2003:97:599-603.
45. Raso G, N'Goran EK, Toty A, et al. Efficacy and side effects of praziquantel against *Schistosoma mansoni* in a community of western Cote d'lvoire. Trans R Soc Trop Med Hyg. 2004:98:18-27.
46. Picquet M, Vercruysse J, Shaw DJ, Diop M, Ly A. Efficacy of praziquantel against *Schistosoma mansoni* in northern Senegal. Trans R Soc Trop Med Hyg. 1998;92:90-3.
47. Degu G, Mengistu G, Jones J. Praziquantel efficacy against S*chistosomiasis mansoni* in schoolchildren in north-west Ethiopia. Trans R Soc Trop Med Hyg. 2002 Jul-Aug;96(4):444-5.
48. Carpio A, Kelvin E, Bagiella E, et al. Effects of albendazole treatment on neurocysticercosis: a randomized controlled trial. J Neurol Neurosurg Psychiatry 2008;79:978.
49. Das K, Mondal G, Banerjee M, et al. Role of antiparasitic therapy for seizures and resolution of lesions in neurocysticercosis patients: an 8 year randomized study. J Clin Neurosci 2007;14:1172-1177.

50. Bildik N, Cevik A, Altintas M, et al. Efficacy of preoperative albendazole use according to months in hydatid cyst of the liver. J Clin Gastroenterol 2007;41:312-316.
51. Wen L, Yan X, Sun F, et al. A randomized, double-blind, multicenter clinical trial on the efficacy of ivermectin against intestinal nematode infections in China. Acta Top 2008;106:190-194.
52. Cleary J, Graham D, Lushbaugh W, et al. Single low-dose mebendazole administered quarterly for ascaris treatment. Am J Med Sci 2007;333:340-45.
53. Flohr C, Tuyen L, Lewis S, et al. Low efficacy of mebendazole against hookworm in Vietnam: two randomized controlled trials. Am J Trop Med Hyg 2007;76:732-736.
54. Hou X, McManus D, Gray D, et al. A randomized, double-blind, placebo-controlled trial of safety and efficacy of combined praziquantel and artemether treatment for acute schistosomiasis japonica in China. Bull World Health Organ 2008;86:788-795.
55. Martins-Leite P, Gazzinelli G, Alves-Oliveira L, et al. Effect of chemotherapy with praziquantel on the production of cytokines and morbidity associated with schistosomiasis mansoni. Antimicrob Agents Chemother 2008;52:2780-2786.
56. Koukounari A, Gabrielli A, Toure S, et al. Schistosoma haematobium infection and morbidity before and after large-scale administration of praziquantel in Burkina Faso. J Infect Dis 2007;196:659-669.
57. Namwanje H, Kabatereine N, Olsen A. A randomised controlled clinical trial on the safety of co-administration of albendazole, ivermectin and praziquantel in infected schoolchildren in Uganda. Trans R Soc Trop Med Hyg 2011;105:181-8.
58. Knopp S, Mohammed KA, Speich B, et al. Albendazole and mebendazole administered alone or in combination with ivermectin against Trichuris trichiura: a randomized controlled trial. Clin Infect Dis 2010;51:1420-8.
59. Olsen A, Namwanje H, Nejsum P, et al. Albendazole and mebendazole have low efficacy against Trichuristrichiura in school-age children in Kabale District, Uganda. Trans R Soc Trop Med Hyg 2009;103:443-6.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Aminoglycosides
AHFS Class 081202
February 8, 2012

I. Overview

The parenteral aminoglycosides are used empirically as monotherapy or in combination with other antibacterial agents to treat serious infections, such as septicemia, respiratory tract infections and complicated urinary tract infections.[1-3] Once susceptibility tests are available and a pathogen has been identified, the aminoglycosides are often discontinued so that treatment with a less toxic agent can be initiated.[5] Neomycin is administered orally as adjunctive therapy to suppress the normal bacterial flora of the bowel to prepare the gastrointestinal tract for surgery.[1-3] It is also used as an adjunctive agent for the treatment of hepatic coma to reduce the ammonia-forming bacteria in the intestinal tract. Tobramycin inhalation solution is approved to improve respiratory symptoms in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*.[4]

The antibacterial properties of aminoglycosides result from both the inhibition of bacterial protein synthesis and the creation of fissures in the outer membrane of the bacterial cell membrane. Irreversible binding to bacterial ribosomes and disruption of the cell membrane results in leakage of intracellular contents and accounts for most of the bactericidal activity.[5-7] The aminoglycosides display concentration-dependent bactericidal activity and a prolonged post-antibiotic effect. They act synergistically when administered with other antibacterial agents.[7] Resistance to the aminoglycosides has been reported infrequently. Amikacin has the broadest spectrum of activity and may be used to treat infections caused by gentamicin- and tobramycin-resistant organisms.[5,8]

The aminoglycosides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the aminoglycosides are available in a generic formulation, with the exception of tobramycin inhalation solution. This class was last reviewed in August 2009.

Table 1. Aminoglycosides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amikacin	injection	N/A	amikacin
Gentamicin	injection	N/A	gentamicin
Kanamycin	injection	N/A	kanamycin
Neomycin	tablet	N/A	neomycin
Streptomycin	injection	N/A	streptomycin
Tobramycin	inhalation solution, injection	TOBI®	tobramycin

PDL=Preferred Drug List
N/A=Not available

The aminoglycosides have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the aminoglycosides that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Aminoglycosides[1-4]

Organism	Amikacin	Gentamicin	Kanamycin	Neomycin	Streptomycin	Tobramycin
Gram-Positive Bacteria						
Enterococcus faecalis					✔	
Staphylococcus species	✔	✔	✔			
Staphylococcus aureus						✔
Streptococcus viridans					✔	
Gram-Negative Bacteria						
Acinetobacter species	✔		✔			
Aerobacter aerogenes					✔	
Brucella species					✔	
Citrobacter species		✔				✔
Enterobacter species	✔	✔		✔		✔
Enterobacter aerogenes			✔			
Escherichia coli	✔	✔	✔	✔	✔	✔
Francisella tularensis					✔	
Haemophilus ducreyi					✔	
Haemophilus influenzae					✔	
Klebsiella species	✔	✔		✔		✔
Klebsiella granulomatis					✔	
Klebsiella pneumoniae			✔		✔	
Morganella morganii						✔
Proteus species	✔	✔	✔		✔	✔
Providencia species	✔					✔
Pseudomonas species	✔					
Pseudomonas aeruginosa		✔				✔
Serratia species	✔	✔				✔
Serratia marcescens			✔			
Yersinia pestis					✔	
Miscellaneous Organisms						
Mycobacterium tuberculosis					✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the aminoglycosides are summarized in Table 3.

Table 3. Treatment Guidelines Using the Aminoglycosides

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Guidelines on the Prevention, Diagnosis, and Treatment of Infective Endocarditis[49] (2009)**	• Antibiotic treatment of infective endocarditis due to oral streptococci and group D streptococci: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin or ceftriaxone for 4 weeks ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for 2 weeks ▪ Vancomycin for 4 weeks (in beta-lactam allergic patients) o Penicillin-resistant strains: ▪ Penicillin G or amoxicillin for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks plus gentamicin for 2 weeks (in beta-lactam allergic patients) • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for 4 to 6 weeks plus gentamicin for 3 to 5 days ▪ Vancomycin for 4 to 6 weeks plus gentamicin for 3 to 5 days (penicillin-allergic patients or methicillin-resistant staphylococci) o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks ▪ Vancomycin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks (penicillin-allergic patients or methicillin-resistant staphylococci) • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains ▪ Amoxicillin plus gentamicin for 4 to 6 weeks ▪ Ampicillin plus gentamicin for 4 to 6 weeks ▪ Vancomycin plus gentamicin for 6 weeks • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months ▪ Doxycycline plus quinolone for >18 months o *Bartonella* species: ▪ Ceftriaxone or ampicillin IV ▪ Doxycycline orally for 6 weeks plus gentamicin or netilmicin for 3 weeks o *Legionella* species: ▪ Erythromycin IV for 2 weeks, then orally for 4 weeks plus rifampin or ciprofloxacin orally for 6 weeks

Clinical Guideline	Recommendation(s)
	o *Mycoplasma* species: ▪ Newer fluoroquinolones for >6 months o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Penicillin G or streptomycin IV for 2 weeks, then cotrimoxazole orally for 1 year ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis (before or without pathogen identification): o Native valves: ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks o Prosthetic valves (early, <12 months post surgery) ▪ Vancomycin IV for 6 weeks, gentamicin IV for 2 weeks, and rifampin orally for 2 weeks o Prosthetic valves (late, ≥12 months post surgery) ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks
American College of Cardiology (ACC)/American Heart Association (AHA): **2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease[50] (2008)**	<u>Endocarditis Prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with CHD o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30-60 minutes before procedure): o Oral: amoxicillin o Unable to take oral medications: Ampicillin, cefazolin or ceftriaxone o Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis* o Penicillin G or ceftriaxone for 4 weeks o Ceftriaxone plus gentamicin for 2 weeks o Vancomycin for 4 weeks in patients allergic to penicillin • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin o Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2

Clinical Guideline	Recommendation(s)
	weeks o Vancomycin for 4 weeks in patients allergic to penicillin • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin o Ampicillin for 4 to 6 weeks or penicillin G plus gentamicin for 4 to 6 weeks o Vancomycin plus gentamicin for 6 weeks in patients allergic to penicillin • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials o Oxacillin-susceptible strains ▪ Nafcillin or oxacillin for 6 weeks plus the optional addition of gentamicin for 3 to 5 days ▪ Cefazolin for 6 weeks with the optional addition of gentamicin in patients allergic to penicillin o Oxacillin-resistant strains ▪ Vancomycin for 6 weeks o Oxacillin-resistant strains • Therapy for prosthetic valve endocarditis caused by staphylococci o Oxacillin-susceptible strains ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks o Oxacillin-resistant strains ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks • Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms o Ceftriaxone for 4 weeks o Ampicillin-sulbactam for 4 weeks o Ciprofloxacin for 4 weeks • Therapy for culture-negative endocarditis including *Bartonella* endocarditis o Native valve ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for 4 to 6 weeks o Prosthetic valve (early; ≤1 year) ▪ Vancomycin for 6 weeks, plus gentamicin for 2 weeks, plus cefepime for 6 weeks, plus rifampin for 6 weeks o Prosthetic valve (late; >1 year) ▪ Suspected *Bartonella*, culture negative • Ceftriaxone for 6 weeks plus gentamicin with/without doxycycline for 6 weeks ▪ Documented *Bartonella*, culture positive • Doxycycline for 6 weeks plus gentamicin for 2 weeks
American Heart Association (AHA): **Infective Endocarditis: Diagnosis, Antimicrobial Therapy, and Management of Complications[16] (2005)**	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus bovis*: o Penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for 4 weeks ▪ Penicillin G or ceftriaxone plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Penicillin-resistant strains:

Clinical Guideline	Recommendation(s)
	▪ Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus bovis*: o Penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for 6 weeks with or without gentamicin for 2 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Penicillin-resistant strains: ▪ Penicillin G or ceftriaxone for 6 weeks plus gentamicin for 6 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for 6 weeks with the option of adding gentamicin for 3-5 days ▪ For penicillin-allergic individuals: cefazolin for 6 weeks with the option of adding gentamicin for 3-5 days o Oxacillin-resistant strains: ▪ Vancomycin for 6 weeks • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) • Therapy for native valve or prosthetic valve enterococcal endocarditis o Strains susceptible to penicillin, gentamicin, and vancomycin: ▪ Ampicillin or penicillin G plus gentamicin for 4-6 weeks ▪ Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Strains susceptible to penicillin, streptomycin, and vancomycin and resistant to gentamicin: ▪ Ampicillin or penicillin G plus streptomycin for 4-6 weeks ▪ Vancomycin plus streptomycin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Strains resistant to penicillin and susceptible to aminoglycosides and vancomycin: ▪ β-lactamase–producing strain: • Ampicillin-sulbactam plus gentamicin for 6 weeks

Clinical Guideline	Recommendation(s)
	• Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for 6 weeks • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin for 4-6 weeks ▪ Vancomycin plus gentamicin plus ciprofloxacin for 4-6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillins) o Prosthetic valve (early, <1 year): ▪ Vancomycin (for 6 weeks) plus gentamicin (for 2 weeks) plus cefepime (for 6 weeks) plus rifampin (for 6 weeks) o Prosthetic valve (late, ≥1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone (for 6 weeks) plus gentamicin (for 2 weeks) with or without doxycycline (for 6 weeks) ▪ Documented *Bartonella*, culture positive: • Doxycycline (for 6 weeks) plus gentamicin for (2 weeks)
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines: Management of Encephalitis[54] (2008)**	Empirical Therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or trimethoprim-sulfamethoxazole is recommended • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; trimethoprim-sulfamethoxazole is an alternative in the penicillin-allergic patient • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered • *Tropheryma whipplei:* ceftriaxone, followed by either trimethoprim-sulfamethoxazole or cefixime, is recommended Rickettsioses and Ehrlichioses • *Anaplasma phagocytophilum:* doxycycline is recommended • *Ehrlichia chaffeensis:* doxycycline is recommended • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended Spirochetes

Clinical Guideline	Recommendation(s)
	• *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative Protozoa • *Acanthamoeba:* trimethoprim-sulfamethoxazole plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; trimethoprim-sulfamethoxazole alone and pyrimethamine plus either atovaquone, clarithromycin, azithromycin, or dapsone are alternatives • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended

European Federation of Neurological Societies (EFNS): **Guideline on the Management of Community-acquired Bacterial Meningitis[13] (2008)**	Empirical Therapy
	• Ceftriaxone 2 g every 12–24 hours or cefotaxime 2 g every 6–8 hours.
	• Alternative therapy: Meropenem 2 g every 8 hours or chloramphenicol 1 g every 6 hours.
	• If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg.
	• Ampicillin/amoxicillin 2 g every 4 hours if *Listeria* is suspected.
	Pathogen Specific Therapy
	• Penicillin-sensitive pneumococcal meningitis:
	  o Benzyl penicillin 250,000 U/kg/day, ampicillin/amoxicillin 2 g every 4 hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every 6–8 hours
	  o Alternative therapy: meropenem 2 g every 8 hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily
	• Pneumococcus with reduced susceptibility to penicillin or cephalosporins:
	  o Ceftriaxone or cefotaxime plus vancomycin ± rifampicin
	  o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin
	• Meningococcal meningitis:
	  o Benzyl penicillin, ceftriaxone, or cefotaxime
	  o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin
	• *Haemophilus influenzae* type B:
	  o Ceftriaxone or cefotaxime
	  o Alternative therapy: chloramphenicol–ampicillin/amoxicillin
	• Listerial meningitis:
	  o Ampicillin or amoxicillin 2 g every 4 hours ± gentamicin 1–2

Clinical Guideline	Recommendation(s)
	mg every 8 hours for the first 7– 10 days o Alternative therapy: trimethoprim–sulfamethoxazole 10–20 mg/kg every 6–12 hours or meropenem • *Staphylococcal* species: o Flucloxacillin 2 g every 4 hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem • Pseudomonal meningitis: o Meropenem ± gentamicin
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Bacterial Meningitis[9] (2004)**	Empiric Therapy • Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative CSF Gram stain result: • Age <1 month: ampicillin plus cefotaxime or ampicillin plus an aminoglycoside Specific Therapy • Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility. • *Pseudomonas aeruginosa* o Standard therapies include cefepime or ceftazidime; alternative therapies include aztreonam, ciprofloxacin, or meropenem (addition of an aminoglycoside should be considered) • *Enterococcus* species o Standard therapy includes ampicillin plus gentamicin
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections[10] (2005)**	Overview • Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first- or second-generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of methicillin-resistant S*taphylococcus aureus* (MRSA) strains. Human Bites • Clenched-fist injuries often require hospitalization and intravenous antimicrobial therapy with agents such as cefoxitin, ampicillin/sulbactam, ertapenem, or some combination that covers *S. aureus, Haemophilus* species, *E. corrodens,* and β-lactamase–producing anaerobes. • *E. corrodens* is usually resistant to first-generation cephalosporins, macrolides, clindamycin, and aminoglycosides, and these agents should be avoided as monotherapy. Necrotizing Infections • Antimicrobial therapy must be directed at the pathogens and used in appropriate doses until repeated operative procedures are no longer needed, the patient has demonstrated obvious clinical improvement, and fever has been absent for 48–72 h. • The best choice of antibiotics for community-acquired mixed infections is a combination of ampicillin-sulbactam plus clindamycin plus ciprofloxacin. The carbapenems, or a combination of cefotaxime plus metronidazole or clindamycin, are also appropriate. In cases of penicillin allergy, alternatives include clindamycin or metronidazole plus an aminoglycoside or fluoroquinolone.

Clinical Guideline	Recommendation(s)
	Surgical Site Infections • If there is minimal surrounding evidence of invasive infection (<5 cm of erythema and induration), and if the patient has minimal systemic signs of infection (a temperature of <38.5°C and a pulse rate of <100 beats/min), antibiotics are unnecessary. • For patients with a temperature of >38.5°C or a pulse rate of >100 beats/min, a short course of antibiotics, usually for a duration of 24–48 h, may be indicated. The antibiotic choice is usually empirical but can be supported by findings of Gram stain and results of culture of the wound contents. • For intestinal or genital tract surgical site infections, single agents such as cefoxitin, ceftizoxime, ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam, or carbapenems are indicated. In cases where facultative and aerobic activity is desired, fluoroquinolones, third-generation cephalosporins, aztreonam, or aminoglycosides are recommended. When anaerobic activity is desired, appropriate treatment includes clindamycin, metronidazole, chloramphenicol or a penicillin agent plus a β-lactamase inhibitor.

Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines[51] (2010)**	Granuloma Inguinale (Donovanosis)
	• Recommended regimen:
	  o Doxycycline 100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed
	• Alternative regimens:
	  o Azithromycin 1 g orally once per week for at least 3 weeks and until all lesions have completely healed
	  o Ciprofloxacin 750 mg orally twice a day for at least 3 weeks and until all lesions have completely healed
	  o Erythromycin base 500 mg orally four times a day for at least 3 weeks and until all lesions have completely healed
	  o Trimethoprim-sulfamethoxazole one double-strength (160 mg/800 mg) tablet orally twice a day for at least 3 weeks and until all lesions have completely healed
	• The addition of an aminoglycoside (e.g., gentamicin 1 mg/kg IV every 8 hours) to these regimens can be considered if improvement is not evident within the first few days of therapy.
	Pelvic Inflammatory Disease
	• Recommended parenteral regimen A:
	  o Cefotetan 2 g IV every 12 hours
	  o Cefoxitin 2 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours
	• Recommended parenteral regimen B:
	  o Clindamycin 900 mg IV every 8 hours plus gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) can be substituted.
	• Alternative parenteral regimens:
	  o Ampicillin/Sulbactam 3 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours
	• Recommended oral regimen:
	  o Ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
	  o Cefoxitin 2 g IM in a single dose and probenecid, 1 g orally administered concurrently in a single dose, plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days

Clinical Guideline	Recommendation(s)
	o Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
Infectious Diseases Society of America (IDSA)/European Society for Microbiology and Infectious Diseases (ESCMID): **International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women[11] (2010)**	Acute Pyelonephritis • Oral ciprofloxacin (500 mg BID) for 7 days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice when resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. A long-acting antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) may replace the initial one time IV ciprofloxacin, and is recommended if the fluoroquinolone resistance is thought to exceed 10%. • Once-daily fluoroquinolones (ciprofloxacin 100 mg extended-release for 7 days, levofloxacin 750 mg for 5 days) is an appropriate choice when resistance to community uropathogens is not known to exceed 10%. If resistance is thought to exceed 10%, an initial intravenous dose of long-acting parenteral antimicrobial (ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral trimethoprim/sulfamethoxazole (160/800 mg BID) for 14 days is an appropriate choice of therapy when the uropathogen is known to be susceptible. If susceptibility is unknown, an initial IV dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral β-lactams are less effective than other available agents for the treatment of pyelonephritis. If an oral β-lactam is used, an initial IV dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • For patients requiring hospitalization, initial treatment with an intravenous antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin with or without an aminoglycoside, or a carbapenem is recommended. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results.
Cystic Fibrosis Foundation (CFF): **Cystic Fibrosis Pulmonary Guidelines[12] (2007)**	Aerosolized Antibiotics • For patients with cystic fibrosis (CF), 6 years of age and older, who have moderate to severe lung disease and with *P. aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin to improve lung function and reduce exacerbations is recommended. • For patients with CF, age 6 years and older who are asymptomatic or with mild lung disease, and with *P. aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin to reduce exacerbations is recommended. • For patients with CF, age 6 years and older, with *P. aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing other chronically inhaled antibiotics (i.e., colistin, gentamicin, ceftazidime) to improve lung function and reduce exacerbations. Macrolide Antibiotics • For patients with CF, 6 years of age and older, and with *P. aeruginosa* persistently present in cultures of the airways, the chronic use of azithromycin to improve lung function and to reduce exacerbations is recommended. Antistaphylococcal Antibiotics

Clinical Guideline	Recommendation(s)
	• For patients with CF, the prophylactic use of oral antistaphylococcal antibiotics to improve lung function and to reduce exacerbations is not recommended.

Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS): **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults**[14] **(2007)**	Empirical Antimicrobial Therapy
	• Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.
	• Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.
	• Inpatient, non-ICU treatment
	  o Respiratory fluoroquinolone
	  o β-lactam plus a macrolide
	• Inpatient, ICU treatment
	  o β-lactam plus either azithromycin or a fluoroquinolone
	  o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam plus either ciprofloxacin or levofloxacin OR
	  o Antipneumococcal, antipseudomonal β-lactam plus an aminoglycoside and azithromycin OR
	  o Antipneumococcal, antipseudomonal β-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone

American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA): **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia**[20] **(2005)**	• Select an initial empiric therapy based on the absence or presence of risk factors for multidrug-resistant (MDR) pathogens. These risk factors include prolonged duration of hospitalization (5 days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy.
	• Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins.
	• In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics.
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for MDR pathogens, early onset, and any disease severity:
	  o Ceftriaxone OR
	  o Levofloxacin, moxifloxacin, ciprofloxacin OR
	  o Ampicillin/sulbactam OR
	  o Ertapenem
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for MDR pathogens and all disease severity – combination antibiotic therapy is recommended as follows:
	  o Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if MRSA risk factors are present or there is a high incidence locally.

World Health Organization (WHO): **Treatment of**	General Treatment Considerations • The essential drugs for the treatment of tuberculosis (TB) include

Clinical Guideline	Recommendation(s)
Tuberculosis[15] (2010)	isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin. They can be dosed daily for 3 times weekly. • Fixed-dose combination products are recommended to help prevent drug resistance. Prescription errors are likely to be less frequent because dosage recommendations are more straightforward, and adjustment of dosage according to patient weight is easier. The number of tablets to ingest is smaller and may encourage patient adherence. • Abbreviations: o H = isoniazid o R= rifampicin o Z = pyrazinamide o E= ethambutol o S = streptomycin <u>New Patients</u> • The 2-month rifampicin regimen (2HRZE/6HE) is associated with more relapses and deaths than the 6-month rifampicin regimen (2HRZE/4HR). • New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin. The standard regimens for new TB patients includes 2 months of HRZE (intensive phase treatment and 4 months of HR (continuation phase). • The 2HRZE/6HE treatment regimen should be phased out. • Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy. • New patients with pulmonary TB may receive a daily intensive phase followed by three times weekly continuation phase [2HRZE/4$(HR)_3$] provided that each dose is directly observed. • Three times weekly dosing throughout therapy [2$(HRZE)_3$/4$(HR)_3$] is another alternative, provided that every dose is directly observed and the patient is not living with HIV or living in an HIV-prevalent setting. • New patients with TB should not receive twice weekly dosing for the full course of treatment unless this is done in the context of formal research. • In populations with known or suspected high levels of isoniazid resistance, new TB patients may receive HRE as therapy in the continuation phase as an acceptable alternative to HR. <u>Standard Regimens for Previously Treated Patients</u> • TB patients whose treatment has failed or other patient groups with high likelihood of multidrug-resistant TB (MDR) should be started on an empirical MDR regimen. • TB patients returning after defaulting or relapsing from their first treatment course may receive the retreatment regimen containing first-line drugs (2HRZES/1HRZE/5HRE)if country-specific data show low or medium levels of MDR in these patients or if such data are not available.
American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC)/Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Treatment of Tuberculosis[19] (2003)**	• Of the approved drugs, isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA) are considered first-line antituberculosis agents and form the core of initial treatment regimens. • Rifabutin and rifapentine may also be considered first-line agents under the specific situations described below. • Streptomycin (SM) was formerly considered to be a first-line agent and, in some instances, is still used in initial treatment; however, an increasing prevalence of resistance to SM in many parts of the world has decreased its overall usefulness. • Because of the relatively high proportion of adult patients with

Clinical Guideline	Recommendation(s)
	tuberculosis caused by organisms that are resistant to isoniazid, four drugs are necessary in the initial phase for the 6-month regimen to be maximally effective. • In most circumstances, the treatment regimen for all adults with previously untreated tuberculosis should consist of a 2-month initial phase of INH, RIF, PZA, and EMB. When drug susceptibility test results are known and the organisms are fully susceptible, EMB need not be included. • For children whose visual acuity cannot be monitored, EMB is usually not recommended except when there is an increased likelihood of the disease being caused by INH-resistant organisms or when the child has "adult-type" (upper lobe infiltration, cavity formation) tuberculosis. • If PZA cannot be included in the initial phase of treatment, or if the isolate is resistant to PZA alone, the initial phase should consist of INH, RIF, and EMB given daily for 2 months. Examples of circumstances in which PZA may be withheld include severe liver disease, gout, and, perhaps, pregnancy. • Although clinical trials have shown that the efficacy of streptomycin (SM) is approximately equal to that of EMB in the initial phase of treatment, the increasing frequency of resistance to SM globally has made the drug less useful. Thus, SM is not recommended as being interchangeable with EMB unless the organism is known to be susceptible to the drug or the patient is from a population in which SM resistance is unlikely. • Streptomycin is the only antituberculosis drug documented to have harmful effects on the human fetus (congenital deafness) and should not be used in pregnancy. • Amikacin and kanamycin are two closely related injectable second-line drugs that are used for patients with drug-resistant tuberculosis whose isolate has demonstrated or presumed susceptibility to the agents. There is nearly always complete cross-resistance between the two drugs, but most SM-resistant strains are susceptible to both. Because it is used to treat a number of other types of infections, amikacin may be more easily obtained, and serum drug concentration measurements are readily available.
Infectious Diseases Society of America (IDSA): **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children**[52] **(2010)**	Community-Acquired Infection in Adults: Mild to Moderate Severity • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*E. Coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections.

Clinical Guideline	Recommendation(s)
	Community-Acquired Infection in Adults: High Severity • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *E. coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E. coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended. • Use of agents effective against MRSA or yeast is not recommended in the absence of evidence of infection due to such organisms. Community-Acquired Infection in Pediatric Patients: • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected MRSA or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. Health Care-Associated Infection: • Therapy should be based on microbiologic results. To achieve empiric coverage, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents.

Clinical Guideline	Recommendation(s)
	Cholecystitis and Cholangitis: • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.
Infectious Diseases Society of America (IDSA): **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus*[53] (2011)**	Skin and Soft-Tissue Infections (SSTIs) • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired (CA) MRSA is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for CA-MRSA is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of CA-MRSA in outpatients with SSTI, oral antibiotic options include the following: clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and CA-MRSA is desired, options include the following: clindamycin alone or TMP-SMX or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of SSTIs is not recommended. • For hospitalized patients with complicated SSTIs, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for MRSA should be considered pending culture data. Options include the following: vancomycin intravenous (IV), linezolid oral (PO) or IV, daptomycin IV, telavancin IV, and clindamycin IV or PO. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to MRSA-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with cSSTIs, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin IV is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative. MRSA Bacteremia and Infective Endocarditis (Native Valve) • For adults with uncomplicated bacteremia, vancomycin or daptomycin IV for at least 2 weeks is recommended. For complicated bacteremia,

Clinical Guideline	Recommendation(s)

	4–6 weeks of therapy is recommended, depending on the extent of infection.
	• For adults with infective endocarditis, IV vancomycin or daptomycin for 6 weeks is recommended.
	• Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis.
	<u>MRSA Bacteremia and Infective Endocarditis (Prosthetic Valve)</u>
	• IV vancomycin plus rifampin PO/IV for at least 6 weeks plus gentamicin IV for 2 weeks.
	• In children, vancomycin IV is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from 2 to 6 weeks depending on source, presence of endovascular infection, and metastatic foci of infection.
	• Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin IV may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus.
	• Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis.
	<u>Management of MRSA Pneumonia</u>
	• For hospitalized patients with severe community-acquired pneumonia, empirical therapy for MRSA is recommended pending sputum and/or blood culture results.
	• For health care–associated MRSA (HA-MRSA) or CA-MRSA pneumonia, IV vancomycin or linezolid PO/IV or clindamycin PO/IV, if the strain is susceptible, is recommended for 7–21 days, depending on the extent of infection.
	• In children, IV vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin IV can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative.
	<u>Management of MRSA Bone and Joint Infections</u>
	• Antibiotics available for parenteral administration include IV vancomycin and daptomycin.
	• Some antibiotic options with parenteral and oral routes of administration include the following: TMP-SMX in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.
	• A minimum 8-week course is recommended. Some experts suggest an additional 1–3 months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with TMP-SMX, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities.
	• For septic arthritis, refer to antibiotic choices for osteomyelitis. A 3 to 4-week course of therapy is suggested.
	<u>Management of MRSA Infections of the CNS</u>
	• Meningitis
	  o IV vancomycin for 2 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid or TMP-SMX.

Clinical Guideline	Recommendation(s)
	o For CNS shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid (CSF) cultures are repeatedly negative. • Brain abscess, subdural empyema, spinal epidural abscess o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and TMP-SMX. • Septic thrombosis of cavernous or dural venous sinus o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and TMP-SMX. o IV vancomycin is recommended in children.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer[21] (2010)**	<u>Initial Antibiotic Therapy</u> • Oral route: o For low-risk adults only; use ciprofloxacin plus amoxicillin-clavulanate • Monotherapy with vancomycin not indicated: o Choose therapy with 1 of the following agents: cefepime or ceftazidime, or imipenem or meropenem • Two drugs without vancomycin: o Choose an aminoglycoside plus antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem • Vancomycin plus 1 or 2 antibiotics: o Choose cefepime or ceftazidime plus vancomycin, with or without an aminoglycoside; carbapenem plus vancomycin, with or without an aminoglycoside; or antipseudomonal penicillin plus an aminoglycoside and vancomycin <u>Modification of Therapy During the First Week of Treatment</u> • Patient becomes afebrile in 3–5 days: o Adjust therapy to the most appropriate drug(s). If no etiologic agent is identified and if the patient is at low risk initially, and oral antibiotic treatment was begun with no subsequent complications, continue use of the same drugs. o If the patient was at low risk initially and therapy with intravenous drugs was begun with no subsequent complications, the regimen may be changed after 48 h to oral ciprofloxacin plus amoxicillin-clavulanate for adults or cefixime for children. o If the patient is at high risk initially with no subsequent complications, continue use of the same intravenous drugs. • Persistent fever throughout the first 3–5 days: o Reassess therapy on day 3. If there is no clinical worsening, continue use of the same antibiotics; stop vancomycin use if cultures do not yield organisms. o If there is progressive disease, change antibiotics. o If the patient is febrile after 5 days, consider adding an antifungal drug <u>Antibiotic Prophylaxis for Afebrile Neutropenic Patients</u> • Use of antibiotic prophylaxis is not routine because of emerging antibiotic resistance, except for the use of trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* pneumonitis.
Working Group on Civilian Biodefense (WGCB): **Plague as a Biological Weapon: Medical and Public Health Management Consensus**	• It is recommended that adults in the contained casualty setting receive a parenteral antibiotic. Preferred parenteral forms of the antimicrobials streptomycin or gentamicin are recommended. • It is recommended that children in the contained casualty setting

Clinical Guideline	Recommendation(s)
Statement[17] (2000)	receive streptomycin or gentamicin. In a mass casualty setting or for postexposure prophylaxis, it is recommended that doxycycline be used. • It is recommended that pregnant women in the contained casualty setting receive gentamicin. Since streptomycin has been associated with rare reports of irreversible deafness in children following fetal exposure, this medication should be avoided if possible. • For adults with pneumonic plague in the mass casualty setting and for postexposure prophylaxis, the preferred treatment choice is doxycycline or ciprofloxacin; the alternative choice is chloramphenicol. • For children with pneumonic plague in the mass casualty setting and for postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin; the alternative choice is chloramphenicol. • For pregnant women with pneumonic plague in the mass casualty setting and for postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin; the alternative choice is chloramphenicol.
Surgical Infection Prevention Guideline Writers Workgroup (SIPGWW): **Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project[18] (2004)**	General Considerations • There is published evidence to support the use of many prophylactic antimicrobial regimens besides those included in this advisory statement or in existing guidelines. • Factors such as cost, half-life, safety, and antimicrobial resistance favor the use of older agents with a relatively narrow spectrum. • The use of newer, broad-spectrum drugs that are front-line therapeutic agents should be avoided in surgical prophylaxis to reduce emergence of bacterial strains that are resistant to these antimicrobials. Gynecologic and Obstetrical Surgery • For abdominal or vaginal hysterectomy, cefotetan is preferred, but reasonable alternatives are cefazolin and cefoxitin. In cases of β-lactam allergy, the workgroup recommends the use of one of the following regimens: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; metronidazole combined with gentamicin or ciprofloxacin; or clindamycin monotherapy. A single 750-mg dose of levofloxacin can be substituted for ciprofloxacin. • For cesarean section, a narrow-spectrum antimicrobial regimen similar to that recommended for hysterectomy provides adequate prophylaxis. Orthopedic Total Joint (Hip and Knee) Arthroplasty • The preferred antimicrobials for prophylaxis in patients undergoing hip or knee arthroplasty are cefazolin and cefuroxime. • Vancomycin or clindamycin may be used in patients with serious allergy or adverse reactions to β-lactams. Cardiothoracic and Vascular Surgery • The recommended antimicrobials for cardiothoracic and vascular operations include cefazolin or cefuroxime. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin is appropriate, and clindamycin may be an acceptable alternative. Colorectal Surgery • Antimicrobial prophylaxis for colorectal operations can consist of an orally administered antimicrobial bowel preparation, a preoperative parenteral antimicrobial, or the combination of both. • Recommended oral prophylaxis consists of neomycin plus erythromycin or neomycin plus metronidazole, initiated no more than 18–24 h before the operation, along with administration of a mechanical bowel preparation.

Clinical Guideline	Recommendation(s)
	• Cefotetan or cefoxitin are recommended for parenteral prophylaxis, and the combination of parenteral cefazolin and metronidazole is also recommended as an alternative. • For patients with confirmed allergy or adverse reaction to β-lactams, use of one of the following regimens is recommended: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; or metronidazole combined with gentamicin or ciprofloxacin. A single 750-mg dose of levofloxacin can be substituted for ciprofloxacin.
American College of Gastroenterology (ACG): **Practice Guidelines: Hepatic Encephalopathy**[55] **(2001)**	Bowel Cleansing • Bowel cleansing is a standard therapeutic measure in hepatic encephalopathy. • Colonic cleansing reduces the luminal content of ammonia, decreases colonic bacterial counts, and lowers blood ammonia in cirrhotic patients. • Various laxatives may be used, but nonabsorbable disaccharides are preferred. • Alternatively, bowel cleansing can also be achieved after irrigation of the gut with isotonic solution of mannitol. Nonabsorbable Disaccharides • Lactulose is a first-line treatment of hepatic encephalopathy. • For acute encephalopathy, lactulose 45 ml is followed by dosing every hour until evacuation occurs. Then dosing is adjusted to achieve two to three soft bowel movements per day (15–45 ml every 8–12 hours). Antibiotics • Antibiotics are a therapeutic alternative to nonabsorbable disaccharides for the treatment of acute and chronic encephalopathy and cirrhosis. • For acute encephalopathy, neomycin (3–6 g/day) should be given for 1-2 weeks. • For chronic encephalopathy, neomycin (1–2 g/day) should be given. Neomycin can be combined with oral lactulose in problematic cases. • Metronidazole should be started at a dose of 250 mg twice daily.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the aminoglycosides are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Aminoglycosides[1-4]

Indication	Amikacin	Gentamicin	Kanamycin	Neomycin	Streptomycin	Tobramycin
Central Nervous System Infections						
Adjunctive therapy in hepatic coma				✔		
Central nervous system infections	✔	✔			✔	✔ *
Dermatological Infections						
Burns	✔	✔				
Skin and skin-structure infections	✔	✔				✔ *
Gastrointestinal Infections						
Gastrointestinal tract infections		✔				
Suppression of the normal bacterial flora of the bowel				✔		
Genitourinary Infections						
Chancroid					✔	
Granuloma inguinale					✔	
Urinary tract infections	✔	✔			✔	✔ *
Respiratory Infections						
Management of cystic fibrosis patients with *P. aeruginosa*						✔ †
Pneumonia					✔	
Respiratory tract infections	✔	✔			✔	✔ *
Tuberculosis					✔	
Miscellaneous Infections						
Bacteremia					✔	
Bone and/or joint infections	✔	✔				✔ *
Brucellosis					✔	
Endocarditis					✔	
Intra-abdominal infections	✔					✔ *
Plague					✔	
Postoperative infections	✔					
Septicemia	✔	✔				✔ *
Serious infections caused by susceptible microorganisms			✔			
Tularemia					✔	

*Injection formulation
†Inhalation formulation

IV. Pharmacokinetics

The pharmacokinetic parameters for the aminoglycosides are summarized in Table 5.

Table 5. Pharmacokinetic Parameters of the Aminoglycosides[1-4]

Generic Name(s)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Amikacin	4-11	Not significant	Renal (90-98)	2
Gentamicin	0-30	Not reported	Renal (70-100)	1.5-4
Kanamycin	0-3	Liver	Renal (81-94)	2.2-2.4
Neomycin	0-88	Not reported	Renal (30-50) Feces (97)	3
Streptomycin	34-35	Not significant	Renal (65)	2.5
Tobramycin	0-30	Not reported	Renal (60-85)	1.6-3

V. Drug Interactions

Significant drug interactions with the aminoglycosides are listed in Table 6.

Table 6. Significant Drug Interactions with the Aminoglycosides[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Aminoglycosides (amikacin, gentamicin, kanamycin, streptomycin, tobramycin)	1	Nondepolarizing muscle relaxants	Aminoglycosides may increase the neuromuscular blocking effects of non-depolarizing muscle relaxants. Prolonged respiratory depression and apnea may occur.
Aminoglycosides (neomycin)	2	Digoxin	The pharmacologic effects of digoxin may be increased or decreased by neomycin.
Aminoglycosides (amikacin, gentamicin, kanamycin, neomycin, streptomycin, tobramycin)	2	Succinylcholine	Neuromuscular blocking effects of succinylcholine may be increased by aminoglycosides. Prolonged respiratory depression with extended periods of apnea may occur.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the aminoglycosides are listed in Table 7. The boxed warnings for the aminoglycosides are listed in Tables 8-9. Ototoxicity and nephrotoxicity are the most serious adverse effects with the aminoglycosides and are most frequently reported in geriatric or dehydrated patients, patients with renal impairment, patients who are receiving high doses or for long periods, those who are also receiving or have received other ototoxic and/or nephrotoxic drugs, and in patients with preexisting tinnitus, vertigo or hearing loss.

Table 7. Adverse Drug Events (%) Reported with the Aminoglycosides[1-4]

Adverse Events	Amikacin	Gentamicin	Kanamycin	Neomycin	Streptomycin	Tobramycin Inhalation Solution	Tobramycin Injection
Cardiovascular							
Chest pain	-	-	-	-	-	26	-
Edema	-	-	✔	-	-	-	-
Hypertension	-	✔	-	-	-	-	-
Hypotension	✔	✔	-	-	-	-	-
Central Nervous System							
Acute organic brain syndrome	-	✔	-	-	-	-	-
Confusion	-	✔	-	-	-	-	✔
Convulsions	-	✔	-	-	-	-	-
Depression	-	✔	-	-	-	-	-
Disorientation	-	-	-	-	-	-	✔
Dizziness	-	✔	-	-	-	6	✔
Drowsiness	-	-	✔	-	-	-	-
Encephalopathy	-	✔	-	-	-	-	-
Fever	✔	✔	-	-	✔	33	✔
Headache	✔	✔	✔	-	-	27	✔
Lethargy	-	✔	-	-	-	6	✔
Malaise	-	-	-	-	-	6	-
Myasthenia gravis-like syndrome	-	✔	-	-	-	-	-
Neuromuscular blockade	✔	-	-	✔	-	-	-
Neurotoxicity	✔	✔	✔	✔	✔	-	✔
Paresthesia	✔	✔	-	-	✔	-	-
Peripheral neuropathy	-	✔	-	-	-	-	-
Pseudotumor cerebri	-	✔	✔	-	-	-	-
Vertigo	-	✔	-	-	✔	-	✔
Dermatological							
Alopecia	-	✔	-	-	-	-	-
Burning	-	✔	✔	-	-	-	-

Adverse Events	Amikacin	Gentamicin	Kanamycin	Neomycin	Streptomycin	Tobramycin Inhalation Solution	Tobramycin Injection
Erythema	-	-	✔	-	-	-	-
Exfoliative dermatitis	-	-	-	-	✔	-	✔
Itching	-	✔	✔	-	-	-	✔
Photosensitivity	-	-	✔	-	-	-	-
Rash	✔	✔	✔	-	✔	5	✔
Redness	-	-	✔	-	-	-	-
Skin tingling	-	✔	-	-	-	-	-
Stinging	-	-	✔	-	-	-	-
Urticaria	-	✔	-	-	✔	-	✔
Gastrointestinal							
Abdominal pain	-	-	-	-	-	13	-
Anorexia	-	-	✔	-	-	19	-
Appetite decreased	-	✔	-	-	-	-	-
Diarrhea	-	-	✔	-	-	6	✔
Enterocolitis	-	-	✔	-	-	-	-
Hemoptysis	-	-	-	-	-	19	-
Malabsorption syndrome	-	-	✔	✔	-	-	-
Nausea	✔	✔	✔	✔	✔	11	✔
Salivation increased	-	✔	✔	-	-	-	-
Sputum discoloration	-	-	-	-	-	21	-
Sputum increased	-	-	-	-	-	38	-
Stomatitis	-	✔	-	-	-	-	-
Taste perversion	-	-	-	-	-	7	-
Vomiting	✔	✔	✔	✔	✔	14	✔
Weight loss	-	✔	✔	-	-	10	-
Genitourinary							
Azotemia	✔	-	-	-	✔	-	-
Cylindruria	✔	✔	-	-	-	-	✔
Hematuria	✔	-	-	-	-	-	-
Nephrotoxicity	-	-	✔	✔	-	-	-
Oliguria	✔	✔	-	-	-	-	✔
Proteinuria	✔	✔	-	-	-	-	✔
Pyuria	✔	-	-	-	-	-	-
Hematologic							
Agranulocytosis	-	✔	✔	-	-	-	-
Anemia	✔	✔	-	-	-	-	✔
Eosinophilia	✔	✔	-	-	✔	-	✔

Adverse Events	Amikacin	Gentamicin	Kanamycin	Neomycin	Streptomycin	Tobramycin Inhalation Solution	Tobramycin Injection
Granulocytopenia	-	✔	✔	-	-	-	✔
Hemolytic anemia	-	-	-	-	✔	-	-
Leukocytosis	-	-	-	-	-	-	✔
Leukopenia	-	✔	-	-	✔	-	✔
Pancytopenia	-	-	-	-	✔	-	-
Reticulocytes decreased	-	✔	-	-	-	-	-
Reticulocytes increased	-	✔	-	-	-	-	-
Thrombocytopenia	-	✔	✔	-	✔	-	✔
Laboratory Test Abnormalities							
AST increased	-	✔	-	-	-	-	✔
ALT increased	-	✔	-	-	-	-	✔
Bilirubin increased	-	✔	-	-	-	-	✔
BUN increased	-	✔	-	-	-	-	✔
Calcium decreased	-	✔	-	-	-	-	✔
LDH increased	-	✔	-	-	-	-	✔
Magnesium decreased	-	✔	-	-	-	-	✔
Potassium decreased	-	✔	-	-	-	-	✔
Serum creatinine increased	✔	✔	-	-	-	3	✔
Sodium decreased	-	✔	-	-	-	-	✔
Musculoskeletal							
Arthralgia	✔	-	-	-	-	-	-
Asthenia	-	-	-	-	-	36	-
Back pain	-	-	-	-	-	7	-
Joint pain	-	✔	-	-	-	-	-
Muscle cramps	-	-	✔	-	-	-	-
Muscle twitching	-	✔	-	-	-	-	-
Tremor	✔	-	✔	-	-	-	-
Weakness	-	-	✔	-	✔	-	-
Respiratory							
Apnea	-	-	-	-	-	-	✔
Asthma	-	-	-	-	-	16	-
Cough increased	-	-	-	-	-	46	-
Dyspnea	-	-	✔	-	-	34	-
Hyperventilation	-	-	-	-	-	5	-
Lower respiratory tract infection	-	-	-	-	-	6	-
Lung disorder	-	-	-	-	-	16-31	-
Pulmonary fibrosis	-	✔	-	-	-	-	-

Adverse Events	Amikacin	Gentamicin	Kanamycin	Neomycin	Streptomycin	Tobramycin Inhalation Solution	Tobramycin Injection
Respiratory depression	-	✔	-	-	-	-	-
Rhinitis	-	-	-	-	-	35	-
Sinusitis	-	-	-	-	-	8	-
Special Senses							
Amblyopia	-	-	-	-	✔	-	-
Ear pain	-	-	-	-	-	7	-
Hearing loss	-	✔	-	-	✔	✔	✔
Ototoxicity	✔	✔	✔	✔	✔	-	✔
Tinnitus	-	✔	-	-	-	3	✔
Visual disturbances	-	✔	-	-	-	-	-
Other							
Anaphylaxis/anaphylactoid reaction	-	✔	-	-	✔	-	-
Angioneurotic edema	-	-	-	-	✔	-	-
Epistaxis	-	-	-	-	-	7	-
Hepatomegaly/splenomegaly	-	✔	-	-	-	-	-
Laryngeal edema	-	✔	-	-	-	-	-
Pain	-	-	-	-	-	8	-
Pain at injection site	-	✔	-	-	-	-	✔
Pharyngitis	-	-	-	-	-	38	-
Purpura	-	✔	-	-	-	-	-
Voice alterations	-	-	-	-	-	13	-

✔ Percent not specified
\- Event not reported

Table 8. Boxed Warning for Parenteral Aminoglycosides[1]

WARNING
Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use. Safety for treatment periods which are longer than 14 days has not been established. **Ototoxicity:** Neurotoxicity, manifested as vestibular and permanent bilateral auditory ototoxicity, can occur in patients with preexisting renal damage and in patients with normal renal function treated at higher doses and/or periods longer than those recommended. The risk of aminoglycoside-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo may occur and may be evidence of vestibular injury. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions. The risk of hearing loss due to aminoglycosides increases with the degree of exposure to either high peak or high trough serum concentrations. Patients developing cochlear damage may not have symptoms during therapy to warn them of developing eighth-nerve toxicity, and total or partial irreversible bilateral deafness may occur after the drug has been discontinued. Aminoglycoside-induced ototoxicity is usually irreversible. **Nephrotoxicity:** Aminoglycosides are potentially nephrotoxic. The risk of nephrotoxicity is greater in patients with impaired renal function and in those who receive high doses or prolonged therapy. **Neuromuscular blockade:** Neuromuscular blockade and respiratory paralysis have been reported following parenteral injection, topical instillation (as in orthopedic and abdominal irrigation or in local treatment of empyema), and following oral use of aminoglycosides. The possibility of these phenomena should be considered if aminoglycosides are administered by any route, especially in patients receiving anesthetics, neuromuscular blocking agents such as tubocurarine, succinylcholine, decamethonium, or in patients receiving massive transfusions of citrate-anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena, but mechanical respiratory assistance may be necessary. **Monitoring:** Renal and eighth-nerve function should be closely monitored especially in patients with known or suspected renal impairment at the onset of therapy and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Serum concentrations of amikacin should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels and prolonged peak concentrations above 35 mcg/ml. Urine should be examined for decreased specific gravity, increased excretion of proteins, and the presence of cells or casts. Blood urea nitrogen, serum creatinine, or creatinine clearance should be measured periodically. Serial audiograms should be obtained where feasible in patients old enough to be tested, particularly high-risk patients. Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss) or nephrotoxicity requires discontinuation of the drug or dosage adjustment. **Concurrent therapy:** Concurrent and/or sequential systemic, oral, or topical use of other neurotoxic or nephrotoxic products, particularly bacitracin, cisplatin, amphotericin B, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin, or other aminoglycosides should be avoided. Other factors that may increase risk of toxicity are advanced age and dehydration. The concurrent use of amikacin with potent diuretics (ethacrynic acid, or furosemide) should be avoided because diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. **Pregnancy:** Aminoglycosides can cause fetal harm when administered to a pregnant woman.

Table 9. Boxed Warning for Neomycin[1]

WARNING
Toxicity: Systemic absorption of neomycin occurs following oral administration, and toxic reactions may occur. Patients treated with neomycin should be under close clinical observation because of the potential toxicity associated with the use of neomycin. Neurotoxicity (including ototoxicity) and nephrotoxicity following the oral use of neomycin sulfate have been reported, even when used in recommended doses. The potential for nephrotoxicity, permanent bilateral auditory ototoxicity, and sometimes vestibular toxicity, is present in patients with healthy renal function when treated with higher doses of neomycin or for longer periods than recommended. Serial, vestibular and audiometric tests, as well as tests of renal function, should be performed (especially in high-risk patients). The risk of nephrotoxicity and ototoxicity is greater in patients with impaired renal function. Ototoxicity is often delayed in onset, and patients developing cochlear damage will not have symptoms during therapy to warn them of developing eighth nerve destruction, and total or partial deafness may occur long after neomycin has been discontinued. Other factors which increase the risk of toxicity are advanced age and dehydration. **Neuromuscular blockage:** Neuromuscular blockage and respiratory paralysis have been reported following the oral use of neomycin. The possibility of the occurrence of neuromuscular blockage and respiratory paralysis should be considered if neomycin is administered, especially to patients receiving anesthetics; neuromuscular-blocking agents such as tubocurarine, succinylcholine, decamethonium; or massive transfusions of citrate anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena, but mechanical respiratory assistance may be necessary. **Concurrent therapy:** Concurrent or sequential systemic, oral or topical use of other aminoglycosides, including paromomycin and other potentially nephrotoxic or neurotoxic drugs such as bacitracin, cisplatin, vancomycin, amphotericin B, polymyxin B, colistin and viomycin, should be avoided because the toxicity may be additive. The concurrent use of neomycin with potent diuretics such as ethacrynic acid or furosemide should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered IV, diuretics may enhance neomycin toxicity by altering the antibiotic concentration in serum and tissue.

VII. Dosing and Administration

The usual dosing regimens for the aminoglycosides are listed in Table 10.

Table 10. Usual Dosing Regimens for the Aminoglycosides[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amikacin	Unspecified Infections: 15 mg/kg/day IM or IV, divided into 2 or 3 equal doses, administered at equally divided intervals; maximum, 15 mg/kg/day or 1.5 g/day (for heavier patients) Urinary Tract Infections (Uncomplicated): 250 mg IM or IV twice daily may be used	Unspecified Infections: Newborns: 10 mg/kg loading dose, followed by 7.5 mg/kg every 12 hours; total daily dose should not exceed 15 mg/kg/day Children and older infants: 15 mg/kg/day IM or IV, divided into 2 or 3 equal doses, administered at equally divided intervals; maximum, 15 mg/kg/day or 1.5 g/day (for heavier patients)	Injection: 100 mg/2 ml 500 mg/2 ml 1,000 mg/4 ml
Gentamicin	Life-Threatening Infections: Up to 5 mg/kg/day IV or IM may be administered in 3 or 4 equal doses. The dose should be	Unspecified Infections: Children: 6 to 7.5 mg/kg/day IV or IM (2 to 2.5 mg/kg every 8 hours)	Injection: 10 mg/ml 20 mg/2 ml 40 mg/ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	reduced to 3 mg/kg/day as soon as clinically indicated Serious Infections: 3 mg/kg/day IV or IM in 3 equal doses every 8 hours Once-Daily Dosing: IV: initial and maintenance, 4 to 7 mg/kg/day IV once every 24 hours; adjust dosage based on serum concentrations	Infants and neonates: 7.5 mg/kg/day IV or IM (2.5 mg/kg every 8 hours) Premature or full-term neonates 1 week of age or younger: 5 mg/kg/day IV or IM (2.5 mg/kg every 12 hours) Preterm infants younger than 32 weeks gestational age: 2.5 mg/kg every 18 hours or 3 mg/kg every 24 hours	60 mg/6 ml 60 mg/50 ml 60 mg/100 ml 70 mg/50 ml 80 mg/8 ml 80 mg/50 ml 80 mg/100 ml 90 mg/100 ml 100 mg/10 ml 100 mg/50 ml 100 mg/0.1 L 120 mg/0.1 L
Kanamycin	Unspecified Infections: IM: 15 mg/kg/day IM in 2 equally divided dosages. If continuously high blood levels are desired, the daily dose of 15 mg/kg may be given in equally divided doses every 6 or 8 hours. IV: 15 mg/kg/day IV divided into 2 or 3 equally divided doses	Unspecified Infections: IM: 15 mg/kg/day IM in 2 equally divided dosages administered at equally divided intervals. If continuously high blood levels are desired, the daily dose of 15 mg/kg may be given in equally divided doses every 6 or 8 hours. IV: 15 mg/kg/day IV divided into 2 or 3 equally divided doses	Injection: 1 g/3 ml
Neomycin	Hepatic Coma: 4-12 g/day in divided doses for 5-6 days; treatment for periods longer than 2 weeks is not recommended Suppression of Intestinal Bacteria: Initial: 1 g orally 19, 18, and 9 hours prior to surgery with oral erythromycin as an adjunct to mechanical cleansing of bowel	Safety and efficacy in children have not been established.	Tablet: 500 mg
Streptomycin	Brucellosis: IM: initial, 1 g/day for 14-21 days (with doxycycline, 100 mg twice a day for 6 weeks) Endocarditis: Streptococcal infections: 1 g twice daily IM for the first week, and 500 mg twice daily IM for the second week in combination with penicillin Enterococcal infections: 1 g twice daily IM for 2 weeks and 500 mg twice daily IM for an additional 4 weeks in combination with penicillin	Unspecified Infections: 20 to 40 mg/kg/day in divided doses every 6 to 12 hours Tuberculosis: 20-40 mg/kg IM once daily, 25-30 mg/kg IM twice weekly, or 25-30 mg/kg IM three times weekly	Injection: 1 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Plague: 2 g/day IM in 2 divided doses for a minimum of 10 days Tuberculosis: 15 mg/kg IM once daily, 25-30 mg/kg IM twice weekly, or 25 to 30 mg/kg IM three times weekly Tularemia: 1 to 2 g daily IM in divided doses for 7 to 14 days until the patient is afebrile for 5 to 7 days Unspecified Infections: 1 to 2 g IM in divided doses every 6 to 12 hours for moderate to severe infections; maximum, 2 g/day		
Tobramycin	Cystic Fibrosis: Inhalation solution: 300 mg administered twice daily for 28 days. After 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle. Life-Threatening Infections: Injection: Up to 5 mg/kg/day IV or IM may be administered in 3 or 4 equal doses. The dosage should be reduced to 3 mg/kg/day as soon as clinically indicated. Once-Daily Dosing: Injection: 4-7 mg/kg IV every 24 hours Serious Infections: Injection: 3 mg/kg/day IV or IM divided in 3 equal doses every 8 hours	Cystic Fibrosis: >6 years of age: Inhalation solution: 300 mg administered twice daily for 28 days. After 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle. Septicemia: ≤1 week of age: Injection: Up to 4 mg/kg/day IV or IM may be administered in 2 equal doses every 12 hours >1 week of age: Injection: 6 to 7.5 mg/kg/day IV or IM in 3 or 4 equally divided doses (2 to 2.5 mg/kg every 8 hours or 1.5 to 1.89 mg/kg every 6 hours)	Inhalation solution: 300 mg/5 ml Injection: 10 mg/ml 40 mg/ml 60 mg/50 ml 80 mg/100 ml 1.2 g

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the aminoglycosides are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Aminoglycosides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cystic Fibrosis				
Ramsey et al.[23] (1999) Tobramycin inhalation solution 300 mg BID for 3 cycles (each cycle consisting of 28 days during which the medication was administered and 28 days during which it was not administered) vs placebo	MC, DB, PC Patients ≥6 years of age with cystic fibrosis, a respiratory tract culture positive for *P. aeruginosa,* ability to perform pulmonary function tests, and FEV_1 25%-75% of predicted value	N=520 24 weeks	Primary: FEV_1 and the density of *P. aeruginosa* in sputum at 20 weeks Secondary: Hospitalization and treatment with intravenous antipseudomonal antibiotics	Primary: At the end of 20 weeks, patients treated with tobramycin inhalation solution had an average 10% increase in FEV_1, as compared to 2% decline for the patients receiving placebo (P<0.001). At the end of 20 weeks, patients treated with tobramycin inhalation solution had an average reduction of 0.8 $\log_{10}$ colony forming units (CFU) per gram of sputum, as compared with the value at 0 weeks, whereas the density in the placebo group had increased by 0.3 $\log_{10}$ CFU per gram (P<0.001). Secondary: Patients receiving tobramycin were 26% less likely to be hospitalized and 36% less likely to require intravenous antipseudomonal antibiotics.
Murphy et al.[24] (2004) Tobramycin inhalation solution (TIS) 300 mg BID for 7 cycles (each cycle consisting of 28 days during which the medication was administered and 28 days during	OL, RCT, PG, MC Patients 6-10 years of age with cystic fibrosis and chronic *P. aeruginosa,* FEV_1 ≥70% and ≤110% of predicted value; patients 11-15 years of age with cystic fibrosis and FEV_1 >70% and <90% of predicted	N=184 56 weeks	Primary: Rate of lung function decline, FEV_1, rates of hospitalization, and concomitant antibiotic use	Primary: Patients treated with tobramycin inhalation solution (TIS) trended toward improvement in percent predicted FEV_1 over control group at weeks 20 and 32, but the improvement was not statistically significant. Significantly fewer TIS patients were hospitalized for worsening of respiratory symptoms (11.0% vs 25.6%; P<0.011), and fewer TIS patients were hospitalized overall (16.5% vs 27.8%; P<0.065). Fewer TIS patients received antibiotics other than the study drug (78.0% vs 95.6%), and significantly fewer patients received oral antibiotics (76.9% vs 91.1%; P<0.009).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
which it was not administered) vs placebo	value			
Quittner et al.[26] (2002) Tobramycin inhalation solution (TIS) 300 mg BID for 28 days for 3 cycles vs placebo	RETRO Patients >6 years of age with cystic fibrosis who were infected with *P. aeruginosa* and had an FEV_1 25%-75% of predicted values	N=520 24 weeks	Primary: Improvement in quality of life	Primary: Patients treated with tobramycin inhalation solution were more likely to report improvement in quality of life than those receiving placebo (P<0.005).
Moss et al.[27] (2002) Tobramycin inhalation solution (TIS) 300 mg BID for 28 days for 3 cycles vs placebo	OL Patients 13 to 17 years of age with cystic fibrosis who were infected with *P. aeruginosa* and had an FEV_1 ≥25% and ≤75% of predicted values	N=128 2 years	Primary: Pulmonary function, *P. aeruginosa* colony-forming unit density, incidence of hospitalization and IV antibiotic use, weight gain	Primary: Patients originally randomized to TIS and placebo treatments exhibited improvements in FEV_1 percent predicted of 13.5% and 9.4%, respectively. Improvement in pulmonary function was significantly correlated with reduction in *P. aeruginosa* colony forming unit density (P=0.0001). The average number of hospitalizations and IV antibiotic courses did not increase over time. TIS treatment was associated with increased weight gain and body mass index (P=0.0002).
Bowman[42] (2002) Tobramycin inhalation solution (TIS) 300 mg BID for 9 cycles (each	OL Patients ≥6 years of age with cystic fibrosis who were infected with *P. aeruginosa* and had	N=396 48 weeks	Primary: Pulmonary function and antibiotic use	Primary: At the start of the open-label study period, the patients who had been receiving TIS continued to show mean FEV_1 values that remained above their baseline values. The patients who were crossed over from placebo to open-label TIS had a marked improvement in their pulmonary function. However, mean FEV_1 in the placebo group did not reach the levels seen in patients who had received with TIS in the initial, double-blind phase.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cycle consisting of 28 days during which the study drug was administered and 28 days during which it was not administered)	an FEV_1 ≥25% and ≤75% of predicted values			By the end of the 12th treatment cycle, the mean FEV_1 in the TIS-only group was 4.7% above the baseline value at the start of the study. Mean FEV_1 at endpoint in patients in the placebo-TIS crossover group was slightly less than the baseline level, but was still greater than it had been at the end of the placebo phase (week 24). In addition to improvement in the FEV_1, patients who were treated with TIS had a significant reduction in the number of courses of IV anti-pseudomonal antibiotic use per year. The patients receiving placebo required 1.9 courses of anti-pseudomonal antibiotics per patient per year, while the patients receiving TIS (both the randomized and the open-label portions of the trial, regardless of initial study group assignment) required approximately 1.25 courses per patient per year. A subgroup analysis was performed evaluating the change in FEV_1 for patients aged 13–17 years. The adolescent patients treated with TIS from the beginning had a marked improvement of approximately 15% in their FEV_1 over the first three cycles of treatment. This contrasts with an approximately 8% decline in FEV_1 for the adolescent patients treated with placebo. The patients who continued TIS maintained their level of improvement over the next nine cycles, ending with an FEV_1 that was still an average of 14.3% above their week 0 baseline after 12 cycles of TIS. The group of adolescent patients who crossed over from the conventional therapy with placebo aerosol to receive TIS in the open-label phase showed a marked improvement during subsequent cycles. This degree of improvement was similar to that seen in the group who started on TIS in the double-blind study. The mean FEV_1 values of this crossover group after nine cycles (72 weeks) of TIS were maintained at levels above those at the start of the open-label part of the study.
Briesacher et al.[44] (2011) Tobramycin inhalation solution (TIS)	RETRO Patients with cystic fibrosis and ≥1 claim for tobramycin	N=804 Variable duration	Primary: Adherence and hospitalization	Primary: Chronic use of TIS was low in patients with *P. aeruginosa* as only 6% were dispensed ≥4 cycles per year. TIS usage was similar for patients with and without the diagnosis of *P. aeruginosa*. In comparison to patients with high utilization of TIS, those using <4

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	inhalation solution			cycles a year were more likely to be hospitalized. High use of TIS was associated with a decreased risk of hospitalization relative to low use (Adjusted odds ratio, 0.40; 95% CI, 0.19-0.84). A higher than average comorbidity risk (AOR, 7.53; 95% CI, 5.20-10.90), a coded diagnosis of *P. aeruginosa* (AOR, 3.0; 95% CI, 2.13-4.32), and a coded diagnosis of failure to thrive/growth failure (AOR, 2.8; 95% CI, 1.09-7.14) were all independently associated with an increased risk of hospitalization.
O'Sullivan et al.[48] (2011) Tobramycin inhalation solution (TIS)	RETRO Patients ≥6 years of age with cystic fibrosis and pulmonary infections	N=1,064 1 year	Primary: Health care utilization	Primary: A higher percentage of children had at least one CF-related office visit (P=0.0046), CF-related outpatient hospital visit (P<0.0001), outpatient hospital visit for any reason (P=0.0016), and CF-related ER visit (P=0.0159) compared to adults. Adults with CF averaged about 12 office visits per year for any diagnosis, compared to about 10 visits per year among children (P=0.0067). Children had more CF-related outpatient hospital visits (P=0.004) as well as prescriptions for TIS (P=0.0007) and dornase alfa (P<0.0001) compared to adult patients. Adults had more frequent inpatient stays for any diagnosis (P=0.0021) and numbers of prescriptions for antibiotics other than TIS and azithromycin compared to children (P=0.0009). Adults had an average of 43 prescriptions per year compared to 39 prescriptions per year for children (P=0.03).
Ratjen et al.[43] (2010) Tobramycin inhalation solution for and additional 28 days (TIS) vs	RCT, OL, MC Patients ≥6 months with cystic fibrosis and early *P. aeruginosa* infection who had already received 28 days of treatment	N=123 56 days	Primary: Median time to recurrence of any strain of *P. aeruginosa* Secondary: Proportion of patients free of *P.*	Primary: The median time to recurrence of *P. aeruginosa* was 26.12 and 25.82 months following TIS for 28 and 56 days, respectively (P=0.593). At the time of each patient's final study visit, 66% of patients remained free of *P. aeruginosa* in the 28-day TIS group and 69% remained free of *P. aeruginosa* in the 56-day TIS group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
discontinuation of tobramycin	with tobramycin inhalation solution		*aeruginosa* 1 month after the end of treatment; time to recurrence of any strain of *P. aeruginosa*; number of patients with the same genotype of *P. aeruginosa* at baseline and recurrence or a new genotype at recurrence; proportion of patients free of *P. aeruginosa* 1 month after the end of treatment for sputum and non-sputum producers and by baseline characteristics, lung function and infection status; number and length of hospital admissions for respiratory indications	The proportion of patients free of *P. aeruginosa* at day 28 and 1 month after the end of treatment was comparable in both groups. The proportion of patients free of *P. aeruginosa* 1 month after the end of treatment was similar in sputum producers and non-sputum producers. Paired samples (baseline and recurrence) were available in 21 patients, of which 12 had the same genotype at baseline and at recurrence. For the remaining patients (n=9), paired samples were of a different genotype. Two patients (5.3%) in the 56-day TIS group were hospitalized on one occasion, each for a pulmonary exacerbation during the study. No major short- or long-term changes in spirometric parameters were observed during the study period.
Hodson et al.[25] (2002) Tobramycin inhalation solution 300 mg BID (TIS)	RCT Patients >6 years of age with cystic fibrosis, FEV_1 >25%; *P.*	N=115 4 weeks	Primary: Mean change from baseline to week 4 in FEV_1 % predicted	Primary: TIS produced a mean 6.7% improvement in lung function (P=0.006), while there was no significant improvement in the colistin-treated patients (mean change 0.37%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs colistin nebulized solution 80 mg inhaled BID	*aeruginosa* positive sputum culture		Secondary: Change in sputum *P. aeruginosa* density, tobramycin/colistin minimum inhibitory concentrations, and safety assessment	Both nebulized antibiotic regimens produced a significant decrease in the sputum *P. aeruginosa* density, and there was no development of highly resistant strains over the course of the study. No significant difference was detected between groups with respect to incidence of adverse events.
Berlana et al.[45] (2011) Tobramycin inhalation solution vs colistin inhalation solution vs tobramycin inhalation solution plus colistin inhalation solution	PRO, OBS Adult patients with cystic fibrosis who received inhaled colistin, inhaled tobramycin or both to treat *P. aeruginosa* bronchial colonization, a history of chronic *P. aeruginosa* bronchial colonization, a diagnosis of bronchiectasis or COPD, and who were receiving long-term treatment (≥12 weeks) of outpatient inhaled antibiotic therapy	N=81 4 years	Primary: Frequency and duration of hospitalizations for respiratory exacerbations Secondary: Emergence of bacterial resistance, antibiotic use during admission, emergence of other opportunistic microorganisms, achievement of sustained *P. aeruginosa* eradication in the airways, mortality, safety, and changes in respiratory function	Primary: Significant differences were observed in the mean yearly rates for hospitalizations, duration of hospitalization, and duration of antibiotic use between the tobramycin and colistin plus tobramycin groups. No significant differences were found in hospitalizations, hospitalization days, or days of antibiotic use between tobramycin and colistin treatment. Secondary: Of the 93 microbiologically assessable antibiotic courses, 10 episodes of *P. aeruginosa* were classified as eradicated, 20 reduced, 17 maintained negative, and 46 no response. Antimicrobial resistance was assessable in 72 episodes. The frequency of emergence of resistant strains differed significantly according to the antibiotic received (48% for tobramycin and 8% for colistin). The highest rate of emergence of other microorganisms was seen in the colistin plus tobramycin group. Only one patient was treated to control persistent isolation of *Aspergillus* species. Neither *P. aeruginosa* eradication nor emergence of other microorganisms was linked to the inhaled antibiotic treatment received. No significant differences were found in the mean change/year in pulmonary function tests between the treatment groups. The overall frequency of patients experiencing an adverse event was 40%. A total of 12 patients (14.8%) died during the study, all for respiratory

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				causes. There were no significant differences in mortality between the study groups, and FEV_1% was linked to mortality (HR, 0.93; 95% CI, 0.86-0.98).
Noah et al.[46] (2010) Tobramycin inhalation solution 300 mg twice daily for 4 weeks (Inhaled Group) vs tobramycin and ceftazidime IV for 2 weeks (Systemic Group)	RCT, SC Children 6 months to 16 years of age with a diagnosis of cystic fibrosis	N=41 Up to 10 weeks	Primary: Change in BALF % neutrophils in the "worst" lobe (%PMN) Secondary: Change in BALF differential cell counts, cytokines, and bacterial quantity	Primary: Worst-lobe %PMN had increased in the Inhaled Group (median Δ%PMN +5.4%) compared to a decrease in the Systemic Group (median Δ%PMN -7.4%). There was no difference between the two treatment regimens (P=0.07). Secondary: The Systemic Group had significantly greater reductions in total cells (-50% vs -3%; P<0.01) and neutrophils (-74% vs -10%; P=0.02) per ml lavage fluid. Macrophages/ml tended to decrease in the Systemic, but not the Inhaled Group. BALF %macrophage values changed in a manner consistent with their inverse correlation with %PMN values: median Δ%PMN declined by 3.0 in the Inhaled Group, and increased by 10.5 in the Systemic Group. Similar but less substantial differential cell count data and changes were obtained from contralateral lobe BALF specimens. The two treatment regimens were also compared in exploratory analyses of relative changes in BALF cytokines and chemokines for the ''worst'' lobe. The tendency for most of these mediators was for a lower ratio in the Systemic Group than in the Inhaled Group (P=0.03 for MIP-1α and P=0.43 for IL-12p40. There was no significant difference in PA cfu/ml and total pathogen cfu/ml in the ''worst'' lobe among the treatment groups (P=0.22 for PA cfu/ml and P=0.45 for total pathogens cfu/ml). Similar outcomes were observed for the contralateral lobe.
Smyth et al.[28] (2005) Tobramycin 10 mg/kg/day IV administered TID	DB, RCT Patients >5 years of age with cystic fibrosis who had a pulmonary	N=244 14 days	Primary: Change in FEV_1 over 14 days of treatment, mean change in baseline FEV_1	Primary: The mean change in FEV_1 (% predicted) over 14 days was similar between the two regimens (10.4% [once daily] vs 10.0% [TID]; adjusted mean difference 0.4% [95% CI: –3.3 to 4.1]). Mean % change in FEV_1 from baseline was also similar in both treatments (21.9% vs 22.1%; –0.1% [–8.0 to 7.9]).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 14 days plus ceftazidime vs tobramycin 10 mg/kg/day IV QD for 14 days plus ceftazidime IV	exacerbation		Secondary: Change in serum creatinine	Secondary: There was no significant difference in % change in creatinine from baseline (–1.5% [once daily] vs 1.7% [TID]). In children, once-daily treatment was significantly less nephrotoxic than TID treatment (mean % change in creatine –4.5% [once daily] vs 3.7% [TID]; adjusted mean difference –8.0%, 95% CI: –15.7 to –0.4), P=0.04.
Miscellaneous Infections				
Evans et al.[22] (1986) Amikacin vs gentamicin vs netilmicin vs sisomicin vs tobramycin	MA, RCT Patients with urinary tract infections, obstetric gynecologic infections, major gram-negative infections, and serious systemic infections	42 trials Variable duration	Primary: Efficacy (bacteriologic or clinical response), nephrotoxicity, auditory toxicity	Primary: Efficacy was an end point in 33 trials. A statistically significant difference was found in only 2 of the 44 aminoglycoside comparisons. These 2 studies noted that sisomicin had greater efficacy than gentamicin. Nephrotoxicity was an end point in all 42 trials. Statistically significant differences were only found for 4 of the 53 aminoglycoside comparisons. Two studies noted a greater risk of nephrotoxicity among patients receiving gentamicin than those receiving amikacin. (Specific details including statistical analyses were not available.) Another study noted that patients receiving gentamicin had a higher risk of nephrotoxicity than those receiving tobramycin. A fourth study noted a higher risk of nephrotoxicity among patients receiving tobramycin than among those receiving netilmicin. Auditory toxicity was an end point in 23 trials. Statistically significant results were found for only 1 of the 32 aminoglycoside comparisons. That study noted a greater risk of auditory toxicity in patients receiving tobramycin than in those receiving netilmicin.
Contopoulos-Ioannidis et al.[32] (2004) Amikacin vs	MA Patients receiving aminoglycosides in different clinical settings (neonatal intensive care unit,	N=995 (24 trials) Variable duration	Primary: Clinical failure rates, microbiologic failure rate and combined clinical or microbiologic	Primary: No significant difference between once-daily dosing (ODD) and multiple-daily dosing (MDD) in the clinical failure rate, microbiologic failure rate, and combined clinical or microbiologic failure rates, but trends favored ODD consistently. A statistically significant benefit was seen with ODD over MDD in trials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
gentamicin vs tobramycin vs netilmicin Multiple-daily dosing (MDD) and once-daily dosing (ODD) for the aminoglycoside classes were compared.	cystic fibrosis, cancer, urinary tract infections, diverse infections, pediatric intensive care units)		failure rates Secondary: Safety endpoints of nephrotoxicity and ototoxicity	using amikacin, whereas no statistical difference was seen in trials using other antibiotics. Secondary: There was no significant difference between ODD and MDD in the primary nephrotoxicity outcomes. Secondary nephrotoxicity outcomes were significantly better with ODD. There was no significant difference between ODD and MDD in the primary ototoxicity outcomes. Studies noting only the clinical impression of hearing impairment also failed to identify any toxicity (ODD: 114 cases; MDD: 114 cases).
King et al.[33] (1992) Amikacin vs tobramycin vs gentamicin	PRO, OS All gram-negative bacilli isolates from any patient source during study period	N=11,641 resistant isolates 64 months	Primary: Resistance, bacteremic episodes, and bacteremia-associated deaths before and after institution of amikacin as the sole preferred aminoglycoside	Primary: Resistance rates to gentamicin, tobramycin, and amikacin among aerobic and facultative gram-negative bacterial isolates were 12.8%, 10.8%, and 5.9%, respectively, before amikacin was adopted as the sole formulary aminoglycoside. After amikacin was adopted as the sole formulary aminoglycoside, over the next 30 months the rates of resistance to gentamicin, tobramycin, and amikacin were 6.3%, 5.0%, and 3.3%, respectively. (P=0.02) During the 30 months when amikacin had preferred status, the incidence of bacteremia-associated death decreased from 18.6% to 11.5% (P=0.003).
Gerding et al.[34] (1991) Amikacin vs	PRO All gram-negative bacilli isolates in a single hospital setting	N=25,000 aerobic and gram-negative bacillary isolates 10 years	Primary: Resistance rates	Primary: Introduction of amikacin at a high level of usage in the 1980's was associated with a significant reduction in resistance to gentamicin and tobramycin among gram-negative bacilli. Gentamicin resistance decreased from 12.0% to 6.4% (P<0.001), tobramycin resistance decreased from 9.5% to 4.8% (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tobramycin vs gentamicin				Rapid introduction of gentamicin usage in 1982 after the use of amikacin was associated with a significant and rapid increase in gentamicin and tobramycin resistance. Gentamicin resistance increased from 6.4% to 9.2% (P<0.001) and tobramycin resistance increased from 4.8% to 6.0% (P<0.05). However, in 1986, gentamicin was again reintroduced to the institution and the usage of gentamicin was gradually increased over a 15-month period without significant change in resistance to gentamicin, tobramycin, or amikacin. Gentamicin resistance decreased from 5.8% to 5.7%, and tobramycin increased from 4.0% to 4.2% (P=not statistically significant).
Skalsky et al.[40] (2008) Aminoglycoside combined with tetracycline vs tetracycline combined with rifampicin or its derivatives vs combination regimens with a quinolone vs combination regimens without quinolones	MA Adults or children with uncomplicated and complicated infections caused by *Brucella* species	30 trials 3-36 months	Primary: Relapse and overall failure Secondary: Therapeutic failure, all-cause mortality, discontinuation of treatment, adverse events	Primary and Secondary: <u>Tetracycline-streptomycin vs tetracycline-rifampicin:</u> Overall failure was significantly higher with tetracycline-rifampicin (RR 2.30, 95% CI: 1.65 to 3.21). Therapeutic failure was higher with tetracycline-rifampicin, but the difference was not significant (RR 1.54; 95% CI: 0.87 to 2.71). Treatment with tetracycline-rifampicin had to be discontinued more often than treatment with tetracycline-streptomycin (RR 1.43; 95% CI:1.03 to 2.00). Adverse events and discontinuation because of adverse events were similar for the two treatment groups (RR 1.08; 95% CI: 0.84 to 1.39, and RR 1.20; 95% CI: 0.40 to 3.59, respectively). <u>Quinolone vs non-quinolone based regimens:</u> Five trials compared quinolone-rifampicin with doxycycline-rifampicin. Overall failure was non-significantly higher in the quinolone group (RR 1.40; 95% CI: 0.77 to 2.52). Both relapse (RR 1.28; 95% CI: 0.64 to 2.53) and therapeutic failure (RR 1.74; 95% CI: 0.59 to 5.19) were more common in the quinolone arm, but this was not significant. The analysis of adverse events favored quinolone-rifampicin (RR 0.37; 95% CI: 0.22 to 0.63). Discontinuation because of adverse events was reported in a single trial, with no significant difference. Two trials compared quinolone-rifampicin with doxycycline-streptomycin. Overall failure was higher in the quinolone arm (RR 2.28; 95% CI: 1.17 to 4.46). Therapeutic failure (RR 1.57; 95% CI: 0.59 to 4.16) occurred more

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs monotherapy vs combination therapy				often with quinolones. There was no difference in rates of adverse events or discontinuation because of adverse events. <u>Monotherapy vs combination treatment regimens:</u> Seven trials assessed monotherapy. The studies were subcategorized according to the type of monotherapy. When co-trimoxazole was the monotherapy, overall failure was not significantly different (RR 1.27; 95% CI: 0.81 to 1.99), though therapeutic failure was more common (RR 2.49; 95% CI: 1.26 to 4.89). For tetracycline monotherapy, the respective relative risks were 1.01 (95% CI: 0.58 to 1.77) and 0.25 (95% CI: 0.03 to 2.32). Two trials assessed six months of cotrimoxazole monotherapy compared with short-term combination therapy (28 days). When the analysis was limited to trials that compared similar durations of treatment for combination treatment and monotherapy, overall failure was more common with monotherapy (RR 2.56; 95% CI: 1.55 to 4.23), while the two trials that compared long monotherapy with short combination therapy found no significant difference.
Sexton et al.[29] (1998) Gentamicin 3 mg/kg once daily plus ceftriaxone 2 g IV QD for 2 weeks vs ceftriaxone 2 g IV QD for 4 weeks	RCT, MC, OL Patients ≥18 years of age with endocarditis who had received <72 hours of parenteral antibiotic therapy	N=51 4 years	Primary: Clinical cure	Primary: Clinical cure was observed for patients both at termination of therapy and at the 3-month follow-up: 25 (96.2%) of the monotherapy patients and 24 (96%) of combination therapy patients were considered clinically cured. Ceftriaxone 2 g QD for 4 weeks and ceftriaxone 2 g QD plus gentamicin 3 mg/kg QD for 2 weeks were both judged effective for treatment of streptococcal endocarditis.
Heldman et al.[30] (1996) Gentamicin 2 mg/kg IV every 8 hours plus oxacillin 2 g IV every 4	RCT, PRO, OL Febrile intravenous drug users with right-sided staphylococcal endocarditis	N=44 28 days	Primary: Bacteriologic evaluation of outcome Secondary: Drug toxicity	Primary: The observed cure rates (18 of 19 [95%] oral vs 22 of 25 [88%] IV) were not statistically distinguishable (OR 0.4. 95% CI: 0.01 to 5.5, P=0.6). Secondary: Drug toxicity was more common in the parenterally treated group (oral 3%, IV 62%; P<0.0001), mostly secondary to oxacillin-associated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours for the first 5 days vs gentamicin 2 mg/kg every 8 hours plus vancomycin 1 g every 12 hours for the first 5 days vs ciprofloxacin 750 mg PO BID plus rifampin 300 mg PO BID				increases in liver enzymes.
Mithani et al.[31] (1996) Gentamicin or tobramycin 1.5 to 2 mg/kg every 8 hours vs gentamicin or tobramycin 6 mg/kg every 24 hours	RETRO All patients who received once-daily aminoglycoside therapy	N=200 1 year	Primary: Rates of clinical response, failure and relapse Secondary: Toxicity	Primary: Eighty-nine patients were cured or improved with once-daily administration versus 90 patients with conventional administration. Secondary: One patient in each group developed definite aminoglycoside-induced renal toxicity.
Song et al.[36] (1998) Gentamicin plus metronidazole	MA Patients scheduled to undergo elective surgery of the colon	147 trials 12 years	Primary: Rate of surgical wound infections	Primary: There was no significant difference in the rate of surgical wound infections between many different regimens. However, certain regimens appeared to be inadequate (e.g., metronidazole alone, doxycycline alone, piperacillin alone, oral neomycin plus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs cefuroxime plus metronidazole vs first generation or second generation cephalosporin vs third generation cephalosporin vs other antibiotic agents as monotherapy or combination therapy				erythromycin on the day before operation). A single dose administered immediately before the operation (or short-term use) was judged as effective as long-term postoperative antimicrobial prophylaxis (OR=1.17; 95% CI: 0.90 to 1.53). There is no convincing evidence to suggest that the new-generation cephalosporins are more effective than first generation cephalosporins (OR 1.07; 95% CI: 0.54 to 2.12).
Mwengee et al.[38] (2006) Gentamicin 2.5 mg/kg IM every 12 hours for 7 days vs doxycycline 100 mg (adults) or 2.2 mg/kg (children) orally every 12 hours for 7 days	RCT, OL Adults and children with symptoms of bubonic, septicemic, or pneumonic plague lasting ≤3 days	N=65 2 weeks	Primary: Efficacy	Primary: Three patients, 2 of whom were treated with gentamicin and 1 of whom was treated with doxycycline, died on the first or second day of treatment, and these deaths were attributed to advanced disease and complications including pneumonia, septicemia, hemorrhage, and renal failure at the start of therapy. All other patients experienced cure or an improved condition after receiving therapy, resulting in favorable response rates of 94% for gentamicin (95% CI: 81.1 to 99.0) and 97% for doxycycline (95% CI: 83.4 to 99.8). *Y pestis* isolates obtained from 30 patients belonged to biotype *antiqua* and were susceptible to gentamicin and doxycycline, which had MICs of 0.13 mg/L and 0.25-0.5 mg/L, respectively. Serum concentrations of antibiotics were within therapeutic ranges, and adverse events were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				infrequent. Patients treated with gentamicin demonstrated a modest increase in the mean serum creatinine concentration after treatment (P<0.05). Both gentamicin and doxycycline were effective therapies for adult and pediatric plague, with high rates of favorable responses and low rates of adverse events.
Roushan et al.[47] (2010) Gentamicin 5 mg/kg once daily for 5 days plus doxycycline 100 mg twice daily for 8 weeks (gentamicin-doxycycline group) vs streptomycin 1 g intramuscularly for 2 weeks plus doxycycline 100 mg twice daily for 45 days (streptomycin-doxycycline group)	RCT Patients >10 years of age with brucellosis	N=164 Up to 8 weeks	Primary: Therapeutic failure due to lack of efficacy and relapse Secondary: Safety	Primary: Therapeutic failure was seen in two (2.4%) patients from the gentamicin-doxycycline group and in four (4.9%) patients from the streptomycin-doxycycline group (P=0.68). Relapse occurred in two (2.4%) patients from the gentamicin- doxycycline group and in five (6.1%) patients from the streptomycin-doxycycline group (P=0.44). Success occurred in 78 (95.12%) patients in the gentamicin-doxycycline group and in 73 (89%) patients in the streptomycin-doxycycline group (P=0.25). Secondary: The rates of adverse effects were similar in the gentamicin-doxycycline group (28%) and in the streptomycin-doxycycline group (22%; P=0.5).
Lewis[35] (2002) Neomycin 2 g orally vs	MA Patients scheduled to undergo elective surgery of the colon	N=215 3 years	Primary: Wound infections	Primary: Wound infections occurred in 5 patients in the combined group (oral and systemic antibiotics) but in 17 of the systemic antibiotic-only group (P<0.01, RR=0.29, 95% CI: 0.11 to 0.75). Bacteria isolated from wound infections and wound fat were more frequent in the colon in the systemic group (P<0.001) and occurred in wound fat in the systemic group twice as often as in the combined group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amikacin 1 g IV vs metronidazole 2 g orally vs metronidazole 1 g IV vs placebo				(P<0.001). The summary weighted risk difference in surgical site infections between groups and the summary risk ratios both favored combined prophylaxis (risk difference=0.56, 95% CI: 0.26 to 0.86; RR=0.51, 95% CI: 0.24 to 0.78; P<0.001).
Boulanger et al.[36] (2004) Streptomycin vs gentamicin vs tetracycline vs gentamicin plus tetracycline	RETRO Patients with plague whose cases were reported in New Mexico during 1985-1999	N=75 N/A	Primary: Mean number of hospital days, fever days, complications, and deaths	Primary: The mean number of fever days after the initiation of antimicrobial treatment was 3.5 days for the streptomycin group, 2.6 days for the gentamicin group, 1.9 days for the gentamicin-tetracycline group and 2.6 days for the tetracycline group (P=0.23). The mean duration of hospital days was 6.2 days in the streptomycin group, 7.2 days in the gentamicin group, and 6.0 days in the gentamicin-tetracycline group (P=0.57). There were no deaths among the 50 patients in the 4 treatment groups. The mean numbers of fever days, hospital days, and complications and the number of deaths did not differ between patients treated with streptomycin and those treated with gentamicin.
Solera et al.[39] (1994) Streptomycin plus doxycycline or	MA Patients with human brucellosis	N=544 (6 trials) Variable duration	Primary: Number of therapeutic failures, number of recurrences, and	Primary: In the rifampin and doxycycline (RD) treatment group, 261 patients were included, with 268 in the streptomycin and doxycycline (SD) group. Five cases of initial therapeutic failure were observed in each group,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
another tetracycline vs rifampin plus doxycycline			total number of cures	without significant differences. Recurrences occurred in 37 patients (16%) in the RD groups and 13 patients (5%) in the SD groups. The Mantel-Haenszel odds ratio on recurrence was 3.81 (95% CI: 1.82 to 8.17; P=0.00009). The total number of cures was 196 (81%) in the RD group and 232 (92%) in the SD group (Mantel-Haenszel odds ratio 0.36; 95% CI: 1.19 to 0.64; P=0.0004).
Kobashi et al.[41] (2007) <u>Group A</u> Streptomycin 15 mg/kg IM three times per week for 3 months plus rifampin 10 mg/kg/day, ethambutol 15 mg/kg/day, and clarithromycin 15 mg/kg/day vs <u>Group B</u> placebo plus rifampin 10 mg/kg/day, ethambutol 15 mg/kg/day, and clarithromycin 15 mg/kg/day	RCT, DB, PC, MC Individuals with positive sputum cultures for *Mycobacterium avium* complex (MAC) without HIV	N=160 24 months	Primary: Microbiological findings, radiological findings, clinical improvement	Primary: The sputum conversion rate for pulmonary MAC disease at the completion of treatment was significantly higher in group A (71.2%) compared with that for group B (50.7%). The clinical improvement was better in group A than in group B with regard to the microbiological findings, underlying respiratory diseases and radiological findings, but there were no significant differences. There was no significant difference in clinical improvement between the two strains of *M. avium* and *M. intracellulare* in groups A and B. There was no significant difference between patients with underlying respiratory diseases and those without them in the two groups. There were no significant differences between the patients in the two groups having a lesion within one-third of the unilateral lung field, within the unilateral lung field, or within the bilateral lung field. There were no significant differences in radiological characteristic findings such as bronchiectasis and cavity between the two groups.

Drug regimen abbreviations: BID=twice daily, IV=intravenous, QD=once daily, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OBS=observational, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=risk ratio, SB=single-blind
Miscellaneous abbreviations: FEV_1=forced expiratory volume

Additional Evidence

Dose Simplification
Once-daily dosing of aminoglycosides is possible due to their rapid concentration-dependent killing and post-antibiotic effect. There was no significant difference between once-daily dosing and multiple daily dosing regimens with regards to clinical failure rates, microbiologic failure rates, or the combined clinical/microbiologic failure rates. Studies have demonstrated that once-daily dosing regimens are as safe as multiple daily dosing regimens with similar efficacy.[7,31-32]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 12. Relative Cost of the Aminoglycosides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amikacin	injection	N/A	N/A	$$$
Gentamicin	injection	N/A	N/A	$$
Kanamycin	injection	N/A	N/A	$$$
Neomycin	tablet	N/A	N/A	$$$
Streptomycin	injection	N/A	N/A	$$$$$
Tobramycin	inhalation solution, injection	TOBI®	$$$$$	$$

*Generic is available in at least one dosage form or strength.
N/A=not available

X. Conclusions

The parenteral aminoglycosides are often used empirically as monotherapy or in combination with other antibacterial agents to treat serious infections, such as septicemia, respiratory tract infections, and complicated urinary tract infections. All of the aminoglycosides are available in a generic formulation, with the exception of tobramycin inhalation solution.

There are many guidelines that define the appropriate place in therapy for the oral/parenteral aminoglycosides. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the aminoglycoside. The parenteral aminoglycosides are recommended as an initial empiric treatment option for serious infections, including acute pyelonephritis, community-acquired pneumonia, nosocomial pneumonia, and febrile neutropenia.[11,14,20-21] They are also recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, encephalitis, meningitis, pelvic inflammatory disease, and plague.[9,13,16-17,49-51,53-54] The aminoglycosides are recommended as an alternative treatment option for skin and soft-tissue infections, granuloma inguinale, tuberculosis, and for surgical prophylaxis.[10,15,18-19,51] Neomycin is recommended for the treatment of hepatic encephalopathy, as well as for the prophylaxis for colorectal surgery.[18,55] Clinical trials have demonstrated comparable efficacy when the oral/parenteral aminoglycosides have been compared to each other, as well as to antibacterial agents in other classes.[22,30-32,36,38-39,41,47]

The chronic use of tobramycin inhalation solution is recommended for patients ≥6 years of age with cystic fibrosis colonized with *P. aeruginosa*, regardless of the severity of lung disease.[12] Treatment with tobramycin has been associated with improvements in pulmonary function, improved quality of life, decreased requirement for intravenous anti-pseudomonal antibiotics, and a decrease in hospitalizations compared to placebo.[23-24,26-27,42,44] Open-label studies following patients for up to 2 years have also demonstrated continued benefit over time.[27,42]

Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity, nephrotoxicity, and neurotoxicity associated with their use.[1] Safety for treatment periods which are longer than 14 days has not been established.

Therefore, all brand aminoglycosides within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Tobramycin inhalation solution has been shown to improve lung function and reduce exacerbations in cystic fibrosis patients colonized with *P. aeruginosa*.[12] Therefore, these patients should be allowed approval for tobramycin inhalation solution through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand aminoglycoside is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2011. Available from Wolters Kluwer Health, Inc. Accessed October 2011.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2011; October 2011.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed October 2011.
4. TOBI® [package insert]. East Hanover, NJ: Novartis; November 2009.
5. Drew RH. Aminoglycosides. In: UpToDate, Hooper, DC (Ed), UpToDate, Waltham, MA, 2011.
6. Khardori N. Antibiotics—Past, Present and Future. Med Clin N Am. 2006;90:1049-76.
7. Chambers H. Aminoglycosides. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. New York: McGraw-Hill: 2006.
8. Burgess D, Abate B. Antimicrobial Regimen Selection. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A Pathophysiologic Approach. 6th Edition. New York: McGraw-Hill; 2005; 1909-19.
9. Tunkel AR, Hartman BJ, Kaplan SL, et al. Infectious Diseases Society of America. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267-84.
10. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, et al. Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005 Nov 15;41(10):1373-406.
11. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20.
12. Flume P, O'Sullivan B, Robinson K, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2007;176:957-969.
13. Chaudhuri A, Martinez-Martin P, Kennedy PG, Andrew Seaton R, Portegies P, Bojar M, Steiner I; EFNS Task Force. EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. Eur J Neurol 2008;15:649-59.
14. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-72.
15. World Health Organization. Treatment of Tuberculosis Guidelines, fourth edition. 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf. Accessed October 2011.
16. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. Circulation. Jun 2005;111:e394-e434.
17. Inglesby TV, Dennis DT, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, et al. Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. JAMA. 2000 May 3;283(17):2281-90.
18. Bratzler DW, Houck PM; Surgical Infection Prevention Guidelines Writers Workgroup, et al. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis. 2004 Jun 15;38(12):1706-15.
19. American Thoracic Society, CDC, and Infectious Diseases Society of America. Treatment of Tuberculosis. MMWR Morb Mortal Wkly Rep 2003;52:RR-11.
20. American Thoracic Society and the Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388–416.
21. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR, Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:e56-93.
22. Evans DA, Buring J, Mayrent S, Rosner B, Colton T, Hennekens C. Qualitative overview of randomized trials of aminoglycosides. Am J Med. 1986 Jun 30;80(6B):39-43.

23. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery BA, Williams-Warren J, et al. Intermittent administration of inhaled tobramcyin in patients with cystic fibrosis. N Engl J Med 1999;341:23-30.
24. Murphy TD, Anbar RD, Lester LA, Nasr SZ, Nickerson B, VanDevanter DR, et al. Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease. Pediatr Pulmonol. 2004;38:314-20.
25. Hodson ME, Gallagher CG, Govan JR. A randomized clinical trial of nebulized tobramycin or colistin in cystic fibrosis. Eur Respir J 2002;20:658-64.
26. Quittner AL, Buu A. Effects of tobramycin solution for inhalation on global ratings on quality of life in patients with cystic fibrosis and Pseudomonas aeruginosa infection. Pediatr Pulmonol. 2002;33:269-76.
27. Moss RB. Long-term benefits of inhaled tobramycin in adolescent patients with cystic fibrosis. Chest. 2002;121(1):55-63.
28. Smyth A, Tan KH, Hyman-Taylor P, Mulheran M, Lewis S, Stableforth D, Prof Knox A. TOPIC Study Group. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis--the TOPIC study: a randomized controlled trial. Lancet. 2005 Feb 12-18;365(9459):573-8.
29. Sexton DJ, Tenenbaum MJ, Wilson WR, Steckelberg JM, Tice AD, Gilbert D, et al. Ceftriaxone once daily for four weeks compared with ceftriaxone plus gentamicin once daily for two weeks for treatment of endocarditis due to penicillin-susceptible streptococci. Endocarditis Treatment Consortium Group. Clin Infect Dis. 1998 Dec;27(6):1470-4.
30. Heldman AW, Hartert TV, Ray SC, Daoud EG, Kowalski TE, Pompili VJ, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med. 1996 Jul ;101(1):68-76.
31. Mithani H, Brown G. The economic impact of once-daily versus conventional administration of gentamicin and tobramycin. Pharmacoeconomics 1996 Nov;10(5):494-503.
32. Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, et al. Extended-interval aminoglycoside administration for children: a meta-analysis. Pediatrics 2004 Jul;114(1):e111-8.
33. King JW, White MC, Todd JR, et al. Alterations in the microbial flora and in the incidence of bacteremia at a university hospital after adoption of amikacin as the sole formulary aminoglycoside. Clin Infect Dis 1992 Apr;14(4):908-15.
34. Gerding DN, Larson TA, Hughes RA, et al. Aminoglycoside resistance and aminoglycoside usage: ten years of experience in one hospital. Antimicrob Agents Chemother 1991 Jul;35(7):1284-90.
35. Lewis RT. Oral versus systemic antibiotic prophylaxis in elective colon surgery: a randomized study and meta-analysis send a message from the 1990s. Can J Surg 2002 Jun;45(3):173-80.
36. Song F, Glenny AM. Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomized controlled trials. Br J Surg 1998 Sep;85(9):1232-41.
37. Boulanger LL, Ettestad P, Fogarty JD, et al. Gentamicin and tetracyclines for the treatment of human plague: review of 75 cases in New Mexico, 1985-1999. Clin Infect Dis 2004 Mar 1;38(5):663-9.
38. Mwengee W. Butler, T. Treatment of plague with gentamicin or doxycycline in a randomized clinical trial in Tanzania. Clin Infect Dis. 2006 Mar 1;42(5):614-21.
39. Solera J, Martinez-Alfaro E, Saez L. Meta-analysis of the efficacy of the combination of rifampin and doxycycline in the treatment of human brucellosis. Med Clin (Barc) 1994 May 21;102(19):731-8.
40. Skalsky K, Yahav D, Bishara J, et al. Treatment of human brucellosis: systematic review and meta-analysis of randomised controlled trials. BMJ 2008;336:701-4.
41. Kobashi Y, Matsushima T, Oka M. A double-blind randomized study of aminoglycoside infusion with combined therapy for pulmonary Mycobacterium avium complex disease. Respir Med 2007;101:130-8.
42. Bowman C. The long-term use of inhaled tobramycin in patients with cystic fibrosis. J Cyst Fibros 2002;1(Suppl 1):194–198.
43. Ratjen F, Munck A, Kho P, et al. Treatment of early Pseudomonas aeruginosa infection in patients with cystic fibrosis: the ELITE trial. Thorax 2010;65:286-91.
44. Briesacher BA, Quittner AL, Saiman L, et al. Adherence with tobramycin inhaled solution and health care utilization. BMC Pulm Med 2011;11:5.
45. Berlana D, Llop JM, Manresa F, et al. Outpatient treatment of Pseudomonas aeruginosa bronchial colonization with long-term inhaled colistin, tobramycin, or both in adults without cystic fibrosis. Pharmacotherapy 2011;31:146-57.
46. Noah TL, Ivins SS, Abode KA, et al. Inhaled versus systemic antibiotics and airway inflammation in children with cystic fibrosis and Pseudomonas. Pediatr Pulmonol 2010;45:281-90.

47. Roushan MR, Amiri MJ, Janmohammadi N, et al. Comparison of the efficacy of gentamicin for 5 days plus doxycycline for 8 weeks versus streptomycin for 2 weeks plus doxycycline for 45 days in the treatment of human brucellosis: a randomized clinical trial. J Antimicrob Chemother 2010;65:1028-35.
48. O'Sullivan AK, Sullivan J, Higuchi K, et al. Health care utilization & costs for cystic fibrosis patients with pulmonary infections. Manag Care 2011;20:37-44.
49. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Eur Heart J 2009;30:2369-413.
50. Bonow R, Carabello B, Chatterjee K et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e1-142.
51. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1-110.
52. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50:133-64.
53. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52:1-38.
54. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM, Whitley RJ, Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303-27.
55. American College of Gastroenterology. Practice guidelines: hepatic encephalopathy. Am J Gastroenterology 2001;96:1968-1976.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cephalosporins
AHFS Class 081206
February 8, 2012

I. Overview

The cephalosporins are approved to treat a variety of infections, including central nervous system, dermatologic, genitourinary, respiratory, as well as several miscellaneous infections.[1-13] They exert their bactericidal action by binding to penicillin-binding proteins, which leads to inhibition of cell-wall synthesis.

The cephalosporins have been shown to be active against a wide range of gram-positive and gram-negative organisms.[1-14] They are frequently grouped into generations based on their spectrum of activity. The first generation cephalosporins (cefadroxil, cefazolin and cephalexin) are most active against gram-positive aerobes with limited activity against gram-negative aerobes. The second generation cephalosporins (cefaclor, cefprozil and cefuroxime) have a greater gram-negative spectrum than first generation agents while retaining some activity against gram-positive cocci. They are also more resistant to beta-lactamases. The third generation cephalosporins (cefdinir, cefditoren, cefixime, cefotaxime, cefpodoxime, ceftazidime, ceftibuten and ceftriaxone) have a broad spectrum of activity and enhanced activity against gram-negative organisms. Cefepime is a fourth generation cephalosporin, which is an extended-spectrum agent with similar activity against gram-positive organisms as first generation cephalosporins. It also has a greater resistance to beta-lactamases than the third generation cephalosporins. Ceftaroline is a fifth generation cephalosporin with a spectrum of activity similar to ceftriaxone. It has greater activity against gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* and vancomycin-intermediate *S. aureus*. Although the concept of "generations" was initially helpful, differences in antimicrobial spectra and pharmacokinetic properties within each generation exist. Additionally, there is an overlap in the spectra between generations.

The cephalosporins that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the cephalosporins are available in a generic formulation with the exception of cefixime, ceftaroline and ceftibuten. This class was last reviewed in August 2009.

Table 1. Cephalosporins Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Cefaclor	capsule, extended-release tablet	N/A	cefaclor
Cefadroxil	capsule, suspension, tablet	N/A	cefadroxil
Cefazolin	injection	N/A	cefazolin
Cefdinir	capsule, suspension	N/A	cefdinir
Cefditoren	tablet	Spectracef®*	cefditoren
Cefepime	injection	N/A	cefepime
Cefixime	suspension, tablet	Suprax®	none
Cefotaxime	injection	Claforan®*	cefotaxime
Cefpodoxime	suspension, tablet	N/A	cefpodoxime
Cefprozil	suspension, tablet	N/A	cefprozil
Ceftaroline	injection	Teflaro®	none
Ceftazidime	injection	Fortaz®*, Fortaz in Iso-Osmotic Dextrose®, Tazicef®*	ceftazidime
Ceftibuten	capsule, suspension	Cedax®	none
Ceftriaxone	injection	Rocephin®*	ceftriaxone
Cefuroxime	injection, suspension, tablet	Ceftin®*, Zinacef®*, Zinacef in Iso-Osmotic Dextrose®, Zinacef in Iso-Osmotic Water®	cefuroxime
Cephalexin	capsule, suspension, tablet	Keflex®*	cephalexin

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

The cephalosporins have been shown to be active against the strains of microorganisms indicated in Tables 2-3. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the cephalosporins that are noted in Table 5. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Cephalosporins[1-13]

Organism	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefixime	Cefotaxime
Gram-Positive Aerobes								
Enterococcus species								✔
Staphylococci	✔	✔						
Staphylococcus aureus	✔		✔	✔	✔	✔		✔
Staphylococcus epidermidis								✔
Streptococci		✔	✔			✔		✔
Streptococcus pneumoniae	✔	✔	✔	✔	✔	✔	✔	✔
Streptococcus pyogenes	✔	✔		✔	✔	✔	✔	✔
Gram-Negative Aerobes								
Acinetobacter species								✔
Citrobacter species								✔
Enterobacter species			✔			✔		✔
Enterococci			✔					
Escherichia coli	✔	✔	✔			✔	✔	✔
Haemophilus influenzae	✔		✔	✔	✔		✔	✔
Haemophilus parainfluenzae				✔	✔			✔
Klebsiella species	✔	✔	✔					✔
Klebsiella pneumoniae						✔		
Moraxella catarrhalis		✔		✔	✔		✔	
Morganella morganii								✔
Neisseria gonorrhoeae							✔	✔
Neisseria meningitidis								✔
Proteus species								✔
Proteus mirabilis	✔	✔	✔			✔	✔	✔
Proteus vulgaris								✔
Providencia rettgeri								✔
Providencia stuartii								✔
Pseudomonas species								✔
Pseudomonas aeruginosa						✔		✔
Serratia marcescens								✔
Anaerobes								

Organism	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefixime	Cefotaxime
Bacteroides species								✔
Bacteroides fragilis						✔		
Clostridium species								✔
Fusobacterium species								✔
Peptococcus species								✔
Peptostreptococcus species								✔

Table 3. Microorganisms Susceptible to the Cephalosporins (cont.)[1-13]

Organism	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Gram-Positive Aerobes								
Staphylococcus aureus	✔	✔		✔		✔	✔	✔
Staphylococcus aureus (including methicillin-resistant isolates)			✔					
Staphylococcus epidermidis						✔		
Staphylococcus saprophyticus	✔							
Streptococci						✔		
Streptococcus agalactiae			✔	✔				
Streptococcus pneumoniae	✔	✔		✔	✔	✔	✔	✔
Streptococcus pyogenes	✔	✔	✔	✔	✔	✔	✔	✔
Gram-Negative Aerobes								
Acinetobacter calcoaceticus						✔		
Citrobacter species				✔				
Enterobacter species				✔		✔		
Enterobacter aerogenes						✔		
Enterobacter cloacae						✔		
Escherichia coli	✔		✔	✔		✔	✔	✔
Haemophilus influenzae	✔	✔	✔	✔	✔	✔	✔	✔
Haemophilus parainfluenzae						✔	✔	
Klebsiella species				✔				
Klebsiella oxytoca			✔			✔		
Klebsiella pneumoniae	✔		✔			✔	✔	✔
Moraxella catarrhalis	✔	✔			✔	✔	✔	✔
Morganella morganii						✔		
Neisseria gonorrhoeae	✔					✔	✔	
Neisseria meningitidis				✔		✔		
Proteus species				✔				
Proteus mirabilis	✔			✔		✔		✔
Proteus vulgaris				✔		✔		

Organism	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Pseudomonas species				✔				
Pseudomonas aeruginosa				✔		✔		
Serratia species				✔				
Serratia marcescens						✔		
Anaerobes								
Bacteroides species				✔				
Bacteroides fragilis						✔		
Clostridium species						✔		
Peptostreptococcus species						✔		
Spirochete								
Borrelia burgdorferi							✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the cephalosporins are summarized in Table 4.

Table 4. Treatment Guidelines Using the Cephalosporins

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Guidelines on the Prevention, Diagnosis, and Treatment of Infective Endocarditis**[143] **(2009)**	• Antibiotic treatment of infective endocarditis due to oral streptococci and group D streptococci: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin or ceftriaxone for 4 weeks ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for 2 weeks ▪ Vancomycin for 4 weeks (in beta-lactam allergic patients) o Penicillin-resistant strains: ▪ Penicillin G or amoxicillin for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks plus gentamicin for 2 weeks (in beta-lactam allergic patients) • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for 4 to 6 weeks plus gentamicin for 3 to 5 days ▪ Vancomycin for 4 to 6 weeks plus gentamicin for 3 to 5 days (penicillin-allergic patients or methicillin-resistant staphylococci) o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks ▪ Vancomycin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks (penicillin-allergic patients or methicillin-resistant staphylococci) • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains ▪ Amoxicillin plus gentamicin for 4 to 6 weeks ▪ Ampicillin plus gentamicin for 4 to 6 weeks ▪ Vancomycin plus gentamicin for 6 weeks • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months ▪ Doxycycline plus quinolone for >18 months o *Bartonella* species: ▪ Ceftriaxone or ampicillin IV ▪ Doxycycline orally for 6 weeks plus gentamicin or netilmicin for 3 weeks o *Legionella* species: ▪ Erythromycin IV for 2 weeks, then orally for 4 weeks plus rifampin or ciprofloxacin orally for 6 weeks

Clinical Guideline	Recommendation(s)
	o *Mycoplasma* species: ▪ Newer fluoroquinolones for >6 months o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Penicillin G or streptomycin IV for 2 weeks, then cotrimoxazole orally for 1 year ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis (before or without pathogen identification): o Native valves: ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks o Prosthetic valves (early, <12 months post surgery) ▪ Vancomycin IV for 6 weeks, gentamicin IV for 2 weeks, and rifampin orally for 2 weeks o Prosthetic valves (late, ≥12 months post surgery) ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks
American College of Cardiology (ACC)/American Heart Association (AHA): **2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease[144] (2008)**	<u>Endocarditis Prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with CHD o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30-60 minutes before procedure): o Oral: amoxicillin o Unable to take oral medications: Ampicillin, cefazolin or ceftriaxone o Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis* o Penicillin G or ceftriaxone for 4 weeks o Ceftriaxone plus gentamicin for 2 weeks o Vancomycin for 4 weeks in patients allergic to penicillin • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin o Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2

Clinical Guideline	Recommendation(s)
	weeks o Vancomycin for 4 weeks in patients allergic to penicillin • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin o Ampicillin for 4 to 6 weeks or penicillin G plus gentamicin for 4 to 6 weeks o Vancomycin plus gentamicin for 6 weeks in patients allergic to penicillin • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials o Oxacillin-susceptible strains ▪ Nafcillin or oxacillin for 6 weeks plus the optional addition of gentamicin for 3 to 5 days ▪ Cefazolin for 6 weeks with the optional addition of gentamicin in patients allergic to penicillin o Oxacillin-resistant strains ▪ Vancomycin for 6 weeks o Oxacillin-resistant strains • Therapy for prosthetic valve endocarditis caused by staphylococci o Oxacillin-susceptible strains ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks o Oxacillin-resistant strains ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks • Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms o Ceftriaxone for 4 weeks o Ampicillin-sulbactam for 4 weeks o Ciprofloxacin for 4 weeks • Therapy for culture-negative endocarditis including *Bartonella* endocarditis o Native valve ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for 4 to 6 weeks o Prosthetic valve (early; ≤1 year) ▪ Vancomycin for 6 weeks, plus gentamicin for 2 weeks, plus cefepime for 6 weeks, plus rifampin for 6 weeks o Prosthetic valve (late; >1 year) ▪ Suspected *Bartonella*, culture negative • Ceftriaxone for 6 weeks plus gentamicin with/without doxycycline for 6 weeks ▪ Documented *Bartonella*, culture positive • Doxycycline for 6 weeks plus gentamicin for 2 weeks
American Heart Association (AHA): **Infective Endocarditis: Diagnosis, Antimicrobial Therapy, and Management of Complications**[38] **(2005)**	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus bovis*: o Penicillin-susceptible strains ▪ Penicillin G or ceftriaxone for 4 weeks ▪ Penicillin G or ceftriaxone plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Penicillin-resistant strains:

Clinical Guideline	Recommendation(s)
	▪ Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus bovis*: o Penicillin-susceptible strains ▪ Penicillin G or ceftriaxone for 6 weeks with or without gentamicin for 2 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Penicillin-resistant strains: ▪ Penicillin G or ceftriaxone for 6 weeks plus gentamicin for 6 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for 6 weeks with the option of adding gentamicin for 3-5 days ▪ For penicillin-allergic individuals: cefazolin for 6 weeks with the option of adding gentamicin for 3-5 days o Oxacillin-resistant strains ▪ Vancomycin for 6 weeks • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) o Oxacillin-resistant strains ▪ Vancomycin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) • Therapy for native valve or prosthetic valve enterococcal endocarditis o Strains susceptible to penicillin, gentamicin, and vancomycin: ▪ Ampicillin or penicillin G plus gentamicin for 4-6 weeks ▪ Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Strains susceptible to penicillin, streptomycin, and vancomycin and resistant to gentamicin: ▪ Ampicillin or penicillin G plus streptomycin for 4-6 weeks ▪ Vancomycin plus streptomycin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Strains resistant to penicillin and susceptible to aminoglycosides and vancomycin: ▪ β-lactamase–producing strain: • Ampicillin-sulbactam plus gentamicin for 6 weeks

Clinical Guideline	Recommendation(s)
	• Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for 6 weeks o Strains resistant to penicillin, aminoglycosides and vancomycin: ▪ *E. faecium*: linezolid or quinupristin-dalfopristin for at least 8 weeks ▪ *E. faecalis*: imipenem/cilastatin plus ampicillin or ceftriaxone plus ampicillin for at least 8 weeks • Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin-sulbactam or ciprofloxacin for 4-6 weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin, gatifloxacin, or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin for 4-6 weeks ▪ Vancomycin plus gentamicin plus ciprofloxacin for 4-6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillins) o Prosthetic valve (early, <1 year): ▪ Vancomycin (for 6 weeks) plus gentamicin (for 2 weeks) plus cefepime (for 6 weeks) plus rifampin (for 6 weeks) o Prosthetic valve (late, ≥1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone (for 6 weeks) plus gentamicin (for 2 weeks) with or without doxycycline (for 6 weeks) ▪ Documented *Bartonella*, culture positive: • Doxycycline (for 6 weeks) plus gentamicin for (2 weeks)
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines: Management of Encephalitis[148] (2008)**	Empirical Therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or trimethoprim-sulfamethoxazole is recommended • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; trimethoprim-sulfamethoxazole is an alternative in the penicillin-

Clinical Guideline	Recommendation(s)
	allergic patient • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered • *Tropheryma whipplei:* ceftriaxone, followed by either trimethoprim-sulfamethoxazole or cefixime, is recommended Rickettsioses and Ehrlichioses • *Anaplasma phagocytophilum:* doxycycline is recommended • *Ehrlichia chaffeensis:* doxycycline is recommended • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative Protozoa • *Acanthamoeba:* trimethoprim-sulfamethoxazole plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; trimethoprim-sulfamethoxazole alone and pyrimethamine plus either atovaquone, clarithromycin, azithromycin, or dapsone are alternatives • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended

European Federation of Neurological Societies (EFNS): **Guideline on the Management of Community-acquired Bacterial Meningitis[15] (2008)**	Empirical Therapy
	• Ceftriaxone 2 g every 12–24 hours or cefotaxime 2 g every 6–8 hours.
	• Alternative therapy: Meropenem 2 g every 8 hours or chloramphenicol 1 g every 6 hours.
	• If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg.
	• Ampicillin/amoxicillin 2 g every 4 hours if *Listeria* is suspected.
	Pathogen Specific Therapy
	• Penicillin-sensitive pneumococcal meningitis:
	  o Benzyl penicillin 250,000 U/kg/day, ampicillin/amoxicillin 2 g every 4 hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every 6–8 hours
	  o Alternative therapy: meropenem 2 g every 8 hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily

Clinical Guideline	Recommendation(s)

	• Pneumococcus with reduced susceptibility to penicillin or cephalosporins:
	  o Ceftriaxone or cefotaxime plus vancomycin ± rifampicin
	  o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin
	• Meningococcal meningitis:
	  o Benzyl penicillin, ceftriaxone, or cefotaxime
	  o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin
	• *Haemophilus influenzae* type B:
	  o Ceftriaxone or cefotaxime
	  o Alternative therapy: chloramphenicol–ampicillin/amoxicillin
	• Listerial meningitis:
	  o Ampicillin or amoxicillin 2 g every 4 hours ± gentamicin 1–2 mg every 8 hours for the first 7– 10 days
	  o Alternative therapy: trimethoprim–sulfamethoxazole 10–20 mg/kg every 6–12 hours or meropenem
	• *Staphylococcal* species:
	  o Flucloxacillin 2 g every 4 hours or vancomycin if penicillin allergy is suspected.
	  o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis.
	• Gram-negative *Enterobacteriaceae*:
	  o Ceftriaxone, cefotaxime or meropenem
	• Pseudomonal meningitis:
	  o Meropenem ± gentamicin

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Bacterial Meningitis[20] (2004)**	<u>Empiric Therapy</u>
	• Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative CSF Gram stain result:
	• Age <1 month: ampicillin plus cefotaxime or ampicillin plus an aminoglycoside
	• Age 1–23 months: vancomycin plus a third-generation cephalosporin
	• Age 2-50 years: vancomycin plus a third-generation cephalosporin
	• Age >50 years: Vancomycin plus ampicillin plus a third-generation cephalosporin
	• Basilar skull fracture: vancomycin plus a third-generation cephalosporin
	• Penetrating head trauma: Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
	• Postneurosurgery: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
	• CSF shunt: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
	<u>Specific Therapy</u>
	• Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility.
	• *Streptococcus pneumoniae*
	  o Penicillin MIC <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapies include ceftriaxone, cefotaxime, or chloramphenicol
	  o Penicillin MIC 0.1-1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include cefepime or meropenem

Clinical Guideline	Recommendation(s)
	o Penicillin MIC ≥2 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime; alternative therapies include gatifloxacin or moxifloxacin o Cefotaxime or ceftriaxone MIC ≥1.0 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime (consider addition of rifampin if MIC of ceftriaxone is >2 µg/mL); alternative therapies include gatifloxacin or moxifloxacin • *Neisseria meningitides* o Penicillin MIC <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapy includes ceftriaxone, cefotaxime or chloramphenicol o Penicillin MIC 0.1- 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include chloramphenicol, a fluoroquinolone or meropenem • *Listeria monocytogenes* o Standard therapy includes ampicillin or penicillin G; alternative therapies include trimethoprim-sulfamethoxazole or meropenem • *Streptococcus agalactiae* o Standard therapy includes ampicillin or penicillin G; alternative therapies include ceftriaxone or cefotaxime • *Escherichia coli* and other enterobacteriaceae o Standard therapy includes a third-generation cephalosporin; alternative therapies include aztreonam, fluoroquinolone, meropenem, trimethoprim-sulfamethoxazole or ampicillin • *Pseudomonas aeruginosa* o Standard therapies include cefepime or ceftazidime; alternative therapies include aztreonam, ciprofloxacin, or meropenem (addition of an aminoglycoside should be considered) • *Haemophilus influenzae* β-lactamase negative strains o Standard therapy includes ampicillin; alternative therapies include ceftriaxone, cefotaxime, cefepime, chloramphenicol or a fluoroquinolone • *Haemophilus influenzae* β-lactamase positive strains o Standard therapy includes a third-generation cephalosporin; alternative therapies include cefepime, chloramphenicol or a fluoroquinolone • *Staphylococcus aureus* methicillin susceptible o Standard therapy includes nafcillin or ofloxacin; alternative therapies include vancomycin or meropenem • *Staphylococcus aureus* methicillin resistant o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapies include trimethoprim-sulfamethoxazole or linezolid • *Staphylococcus epidermidis* o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapy includes linezolid • *Enterococcus* species ampicillin susceptible o Standard therapy includes ampicillin plus gentamicin • *Enterococcus* species ampicillin resistant o Standard therapy includes vancomycin plus gentamicin • *Enterococcus* species ampicillin and vancomycin resistant o Standard therapy includes linezolid

Clinical Guideline	Recommendation(s)

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections[34] (2005)**	Overview
	• Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first- or second-generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of methicillin-resistant S*taphylococcus aureus* (MRSA) strains.
	Animal Bites
	• Oral treatment options
	  o Amoxicillin/clavulanate is recommended.
	  o Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin.
	  o Other options, including fluoroquinolones, trimethoprim-sulfamethoxazole, and cefuroxime, may require an additional agent active against anaerobes, such as metronidazole or clindamycin.
	  o First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *P. multocida* and should be avoided.
	• Intravenous treatment options
	  o β-lactam/β-lactamase combinations, piperacillin/tazobactam, second-generation cephalosporins, and carbapenems.
	  o Second-generation and third-generation cephalosporins may be used but may require the addition of an anti-anaerobic agent.
	Animal Contact
	• Erysipeloid:
	  o For cutaneous infection, penicillin or amoxicillin for 7–10 days seems to be rational.
	  o For patients who are intolerant of penicillins, treatment with cephalosporins, clindamycin, or fluoroquinolones should be effective.
	Cellulitis
	• A large percentage of patients can receive oral medications from the start. Suitable agents include dicloxacillin, cephalexin, clindamycin, or erythromycin, unless streptococci or staphylococci.
	• For parenteral therapy, which is indicated for severely ill patients or for those unable to tolerate oral medications, reasonable choices include a penicillinase-resistant penicillin such as nafcillin, a first-generation cephalosporin such as cefazolin, or, for patients with life-threatening penicillin allergies, clindamycin or vancomycin.
	• In cases of uncomplicated cellulitis, 5 days of antibiotic treatment is as effective as a 10-day course.
	Erysipelas
	• Penicillin, given either parenterally or orally depending on clinical severity, is the treatment of choice.
	• If staphylococcal infection is suspected, a penicillinase-resistant semisynthetic penicillin or a first-generation cephalosporin should be selected.
	Human Bites
	• Clenched-fist injuries often require hospitalization and intravenous antimicrobial therapy with agents such as cefoxitin, ampicillin/sulbactam, ertapenem, or some combination that covers *S. aureus, Haemophilus* species, *E. corrodens,* and β-lactamase–producing anaerobes.
	• *E. corrodens* is usually resistant to first-generation cephalosporins, macrolides, clindamycin, and aminoglycosides, and these agents

Clinical Guideline	Recommendation(s)
	should be avoided as monotherapy. • In the type 1 β-lactam–allergic patient, fluoroquinolones plus clindamycin, or trimethoprim-sulfamethoxazole plus metronidazole may be useful. Impetigo • The decision of how to treat impetigo depends on the number of lesions, their location (face, eyelid, or mouth), and the need to limit spread of infection to others. • Patients who have numerous lesions or who are not responding to topical agents should receive oral antimicrobials effective against both *S. aureus* and *S. pyogenes.* • Because *S. aureus* currently accounts for most cases of bullous impetigo, as well as for a substantial portion of nonbullous infections, penicillinase-resistant penicillins or first generation cephalosporins are preferred. • Erythromycin has been a mainstay of pyoderma therapy, but its utility may be lessened in areas where erythromycin-resistant strains of *S. aureus,* or more recently. • Additional therapies include clindamycin or amoxicillin/clavulanate. Necrotizing Infections • Antimicrobial therapy must be directed at the pathogens and used in appropriate doses until repeated operative procedures are no longer needed, the patient has demonstrated obvious clinical improvement, and fever has been absent for 48–72 h. • The best choice of antibiotics for community-acquired mixed infections is a combination of ampicillin-sulbactam plus clindamycin plus ciprofloxacin. The carbapenems, or a combination of cefotaxime plus metronidazole or clindamycin, are also appropriate. In cases of penicillin allergy, alternatives include clindamycin or metronidazole plus an aminoglycoside or fluoroquinolone. • *S aureus* infection, often associated with pyomyositis, should be treated with nafcillin, oxacillin, or cefazolin. Vancomycin should be reserved for resistant strains or can be used in cases of severe penicillin allergy, as well as linezolid, quinupristin-dalfopristin or daptomycin. Clindamycin is limited by its potential of cross-resistance. Surgical Site Infections • If there is minimal surrounding evidence of invasive infection (<5 cm of erythema and induration), and if the patient has minimal systemic signs of infection (a temperature of <38.5°C and a pulse rate of <100 beats/min), antibiotics are unnecessary. • For patients with a temperature of >38.5°C or a pulse rate of >100 beats/min, a short course of antibiotics, usually for a duration of 24–48 h, may be indicated. The antibiotic choice is usually empirical but can be supported by findings of Gram stain and results of culture of the wound contents. • For intestinal or genital tract surgical site infections, single agents such as cefoxitin, ceftizoxime, ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam, or carbapenems are indicated. In cases where facultative and aerobic activity is desired, fluoroquinolones, third-generation cephalosporins, aztreonam, or aminoglycosides are recommended. When anaerobic activity is desired, appropriate treatment includes clindamycin, metronidazole, chloramphenicol or a penicillin agent plus a β-lactamase inhibitor. • In axillary or perineum surgical site infections, cefoxitin, ampicillin-sulbactam or agents indicated for intestinal and genital sites are

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	appropriate.
Infectious Diseases Society of America (IDSA): **Diagnosis and Treatment of Diabetic Foot Infections**[147] **(2004)**	• Empirical antibiotic regimens should be based on the clinical severity of the infection. • Current clinical data does not allow for the recommendation of any specific antibiotic regimen for diabetic foot infections (DFIs). • Suggested agents are derived from available published clinical trials and expert experience. • Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have US Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid is currently specifically approved for diabetic foot infections. • Suggested empirical antibiotic regimens for mild infections: dicloxacillin, clindamycin, cephalexin, trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, levofloxacin • Suggested empirical antibiotic regimens for moderate infections: trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, levofloxacin, cefoxitin, ceftriaxone, ampicillin/sulbactam, linezolid (with or without aztreonam), daptomycin (with or without aztreonam), ertapenem, cefuroxime (with or without metronidazole), ticarcillin/clavulanate, piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin • Suggested empirical antibiotic regimens for severe infections: piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin, imipenem-cilastatin, vancomycin and ceftazidime (with or without metronidazole)

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Infectious Diarrhea**[149] **(2001)**	<u>Recommendations for Therapy Against Specific Pathogens</u>
	• *Shigella* species:
	  o Trimethoprim-sulfamethoxazole (TMP-SMZ)
	  o Fluoroquinolone
	  o Nalidixic acid
	  o Ceftriaxone
	  o Azithromycin
	• *Salmonella,* non-typhi species:
	  o Treatment is not routinely recommended; however, consider therapy in patients <6 months old or >50 years old, or patients that have a prosthesis, valvular heart disease, severe atherosclerosis, malignancy, or uremia.
	  o TMP-SMZ
	  o Fluoroquinolone
	• *Campylobacter* species
	  o Erythromycin
	• *Escherichia coli* species
	  o TMP-SMZ
	  o Fluoroquinolone
	• *Aeromonas* or *Plesiomonas* species
	  o TMP-SMZ
	  o Fluoroquinolone
	• *Yersinia* species
	  o Antibiotic therapy is not usually required. For severe infections or associated bacteremia, combination therapy with doxycycline, aminoglycosides TMP-SMZ or a fluoroquinolone is recommended.

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	• *Vibrio cholerae*
	  o Doxycycline or tetracycline
	  o Fluoroquinolone
	• Toxigenic *Clostridium difficile*
	  o Metronidazole
	• *Isospora* species
	  o TMP-SMZ
	• *Cyclospora* species
	  o TMP-SMZ

Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines[16] (2010)**	<u>Chancroid</u>
	• Recommended regimens:
	  o Azithromycin 1 g orally in a single dose
	  o Ceftriaxone 250 mg intramuscularly (IM) in a single dose
	  o Ciprofloxacin 500 mg orally twice a day for 3 days
	  o Erythromycin base 500 mg orally three times a day for 7 days
	<u>Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum</u>
	• Recommended regimens:
	  o Ceftriaxone 250 mg IM in a single dose
	  o Cefixime 400 mg orally in a single dose
	  o Single-dose injectable cephalosporin regimens plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for 7 days
	<u>Uncomplicated Gonococcal Infections of the Pharynx</u>
	• Recommended regimens:
	  o Ceftriaxone 250 mg IM in a single dose plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for 7 days
	<u>Gonococcal Conjunctivitis</u>
	• Recommended regimen:
	  o Ceftriaxone 1 g IM in a single dose
	<u>Disseminated Gonococcal Infection</u>
	• Recommended regimen:
	  o Ceftriaxone 1 g IM or IV every 24 hours
	• Alternative regimens:
	  o Cefotaxime 1 g IV every 8 hours
	  o Ceftizoxime 1 g IV every 8 hours
	<u>Gonococcal Meningitis and Endocarditis</u>
	• Recommended regimen:
	  o Ceftriaxone 1–2 g IV every 12 hours
	<u>Gonococcal Infections Among Children</u>
	• Recommended regimen for children >45 kg:
	  o Treat with one of the regimens recommended for adults
	• Recommended regimen for children who weigh ≤45 kg and who have uncomplicated gonococcal vulvovaginitis, cervicitis, urethritis, pharyngitis, or proctitis:
	  o Ceftriaxone 125 mg IM in a single dose
	• Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis:
	  o Ceftriaxone 50 mg/kg (maximum dose: 1 g) IM or IV in a single dose daily for 7 days
	• Recommended regimen for children who weigh >45 kg and who have bacteremia or arthritis:
	  o Ceftriaxone 50 mg/kg IM or IV in a single dose daily for 7 days
	<u>Pelvic Inflammatory Disease</u>

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	• Recommended parenteral regimen A:
	  o Cefotetan 2 g IV every 12 hours
	  o Cefoxitin 2 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours
	• Recommended parenteral regimen B:
	  o Clindamycin 900 mg IV every 8 hours plus gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) can be substituted.
	• Alternative parenteral regimens:
	  o Ampicillin/Sulbactam 3 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours
	• Recommended oral regimen:
	  o Ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
	  o Cefoxitin 2 g IM in a single dose and probenecid, 1 g orally administered concurrently in a single dose, plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
	  o Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
	<u>Epididymitis</u>
	• Recommended regimens :
	  o Ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg orally twice a day for 10 days
	• For acute epididymitis most likely caused by enteric organisms:
	  o Levofloxacin 500 mg orally once daily for 10 days
	  o Ofloxacin 300 mg orally twice a day for 10 days
	<u>Proctitis, Proctocolitis, and Enteritis</u>
	• Recommended regimen:
	  o Ceftriaxone 250 mg IM plus doxycycline 100 mg orally twice a day for 7 days

Infectious Diseases Society of America (IDSA)/European Society for Microbiology and Infectious Diseases (ESCMID): **International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women[36] (2010)**	<u>Acute Uncomplicated Bacterial Cystitis</u> • Nitrofurantoin monohydrate/macrocrystals (100 mg BID for 5 days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage. • Trimethoprim-sulfamethoxazole (160/800 mg BID for 3 days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible. • Fosfomycin (3 g in a single dose) is an appropriate choice for therapy where it's available due to minimal resistance and propensity for collateral damage, but it appears to be less effective compared to standard short-course regimens. • Ofloxacin, ciprofloxacin and levofloxacin are highly efficacious in 3-day regimens, but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis. • β-lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in 3-7 day regimens are appropriate choices for therapy when other recommended agents cannot be used. Other β-

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	lactams, such as cephalexin are less well studied, but may also be appropriate in certain settings. The β-lactams are generally less effective and have more adverse effects compared with other UTI antimicrobials. For these reasons, β-lactams should be used with caution for uncomplicated cystitis. • Amoxicillin or ampicillin should not be used for empirical treatment given the relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. Acute Pyelonephritis • Oral ciprofloxacin (500 mg BID) for 7 days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice when resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. A long-acting antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) may replace the initial one time IV ciprofloxacin, and is recommended if the fluoroquinolone resistance is thought to exceed 10%. • Once-daily fluoroquinolones (ciprofloxacin 100 mg extended-release for 7 days, levofloxacin 750 mg for 5 days) is an appropriate choice when resistance to community uropathogens is not known to exceed 10%. If resistance is thought to exceed 10%, an initial intravenous dose of long-acting parenteral antimicrobial (ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral trimethoprim/sulfamethoxazole (160/800 mg BID) for 14 days is an appropriate choice of therapy when the uropathogen is known to be susceptible. If susceptibility is unknown, an initial IV dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral β-lactams are less effective than other available agents for the treatment of pyelonephritis. If an oral β-lactam is used, an initial IV dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • For patients requiring hospitalization, initial treatment with an intravenous antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin with or without an aminoglycoside, or a carbapenem is recommended. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results.
American College of Obstetricians and Gynecologists (ACOG): **Treatment of Urinary Tract Infections in Nonpregnant Women[19] (2008)**	• For uncomplicated acute bacterial cystitis, recommended treatment regimens are as follows: o Trimethoprim–sulfamethoxazole: 1 tablet (160 mg trimethoprim–800 mg sulfamethoxazole) twice daily for 3 days. o Trimethoprim 100 mg twice daily for 3 days. o Ciprofloxacin 250 mg twice daily for 3 days, levofloxacin 250 mg once daily for 3 days, norfloxacin 400 mg twice daily for 3 days, or gatifloxacin 200 mg, once daily for 3 days. o Nitrofurantoin macrocrystals 50 to 100 mg 4 times daily for 7 days, or nitrofurantoin monohydrate 100 mg twice daily for 7 days. o Fosfomycin tromethamine, 3-g dose (powder) single dose.
American Academy of Pediatrics (AAP)/American Academy of Family Physicians (AAFP): **Diagnosis and Management of Acute Otitis Media[25]**	Observation Option • Observation without use of antibacterial agents in a child with uncomplicated acute otitis media (AOM) is an option for selected children based on diagnostic certainty, age, illness severity, and

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(2004)	assurance of follow-up. The "observation option" for AOM refers to deferring antibacterial treatment of selected children for 48 to 72 hours and limiting management to symptomatic relief. This option should be limited to otherwise healthy children 6 months to 2 years of age with non-severe illness at presentation and an uncertain diagnosis and to children 2 years of age and older without severe symptoms at presentation or with an uncertain diagnosis. Antibacterial Options - Temperature <39°C Without Severe Otalgia • Initial Treatment With Antibacterial Agents o Recommended agent ▪ Amoxicillin 80-90 mg/kg/day o Alternative for penicillin allergy ▪ Non-type I: cefdinir, cefuroxime, cefpodoxime ▪ Type I: azithromycin, clarithromycin • Treatment failure at 48-72 hours after initial management with observation option o Recommended agent ▪ Amoxicillin 80-90 mg/kg/day o Alternative for penicillin allergy ▪ Non-type I: cefdinir, cefuroxime, cefpodoxime ▪ Type I: azithromycin, clarithromycin • Treatment failure at 48-72 hours after initial management with antibacterial agents o Recommended agent ▪ Amoxicillin-clavulanate (90 mg/kg/day of amoxicillin component, with 6.4 mg/kg/day of clavulanate). o Alternative for penicillin allergy ▪ Non-type I: ceftriaxone for 3 days ▪ Type I: clindamycin Antibacterial Options - Temperature ≥39°C and/or Severe Otalgia • Initial treatment with antibacterial agents o Recommended agent ▪ Amoxicillin-clavulanate (90 mg/kg/day of amoxicillin component, with 6.4 mg/kg/day of clavulanate). o Alternative for penicillin allergy ▪ Ceftriaxone for 1 or 3 days • Treatment failure at 48-72 hours after initial management with observation option o Recommended agent ▪ Amoxicillin-clavulanate (90 mg/kg/day of amoxicillin component, with 6.4 mg/kg/day of clavulanate). o Alternative for penicillin allergy ▪ Ceftriaxone for 1 or 3 days • Treatment failure at 48-72 hours after initial management with antibacterial agents o Recommended agent ▪ Ceftriaxone for 3 days o Alternative for penicillin allergy ▪ Tympanocentesis, clindamycin
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Group A**	• Patients with acute streptococcal pharyngitis should receive therapy with an antimicrobial agent in a dose and for a duration that is likely to eradicate the infecting organism from the pharynx. • Penicillin remains the agent of choice because of its proven efficacy,

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Streptococcal Pharyngitis[28] (2002)	safety, and narrow spectrum. • Amoxicillin is often used in place of oral penicillin V to treat young children; the efficacy appears to be equal. This choice is primarily related to acceptance of the taste of the suspension. • Intramuscular administration of benzathine penicillin G is preferred for patients who are unlikely to complete a full 10- day course of oral therapy. • Erythromycin is a suitable alternative for patients allergic to penicillin. • First-generation cephalosporins are also acceptable for patients who do not exhibit immediate-type hypersensitivity to β-lactam antibiotics. • Most oral antibiotic therapy must be administered for the conventional 10 days to achieve maximal rates of pharyngeal eradication of group A streptococci. • When multiple episodes occur over the course of months or years, it may be difficult to differentiate viral pharyngitis in a *Streptococcus* carrier from true group A streptococcal pharyngitis. Therapy with certain antimicrobial agents, such as clindamycin and amoxicillin-clavulanate, may be beneficial, because they have been shown to yield high rates of eradication of streptococci from the pharynx under these particular circumstances.
American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF): **Clinical Practice Guideline: Adult Sinusitis[17] (2007)**	Symptomatic Relief of Viral Rhinosinusitis (VRS) • Management of VRS is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Topical or systemic decongestants may offer additional symptomatic relief. • Antihistamines have been used to treat VRS due to their drying effect; however, no studies have been published that assess the impact of antihistamines specifically on VRS outcomes. Adverse effects of antihistamines, especially first-generation H_1-antagonists, include drowsiness, behavioral changes, and impaired mucus transport in the nose and sinuses because of drying. Symptomatic Relief of Acute Bacterial Rhinosinusitis (ABRS) • Symptomatic treatments for ABRS include decongestants, corticosteroids, saline irrigation, and mucolytics. None of these products have been approved by the FDA for use in acute rhinosinusitis, and few have data from controlled clinical studies supporting this use. • Antihistamines have no role in the symptomatic relief of ABRS in nonatopic patients. There are no studies that support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. • Antihistamines may be considered in patients with ABRS whose symptoms suggest a significant allergic component. Watchful Waiting for Acute Bacterial Rhinosinusitis (ABRS) • Observation without use of antibiotics is an option for selected adults with uncomplicated ABRS who have mild illness (mild pain and temperature <38.3°C or 101°F). Choice of Antibiotic for Acute Bacterial Rhinosinusitis (ABRS) • If a decision is made to treat ABRS with an antibiotic, the clinician should prescribe amoxicillin as first-line therapy for most adults. Treatment Failure for Acute Bacterial Rhinosinusitis (ABRS) • If the patient worsens or fails to improve with the initial management option by 7 days after diagnosis, the clinician should reassess the patient to confirm ABRS, exclude other causes of illness, and detect complications.

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	• If ABRS is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI): **Diagnosis and Management of Sinusitis: An Updated Practice Parameter**[26] **(2005)**	• Antibiotics are the primary therapy for bacterial sinusitis. • The most common bacteria observed in acute sinusitis, recurrent acute sinusitis, and acute exacerbations of chronic sinusitis are *S pneumoniae*, *H influenzae*, and *M catarrhalis*. • Choice of antibiotic should be based on predicted effectiveness and side effects. • Amoxicillin is a reasonable initial antibiotic choice in both children and adults with uncomplicated disease. • Trimethoprim-sulfamethoxazole can be used as an alternative drug in adults. Resistance is more commonly seen in children, and it is recommended that the clinician refer to their local biogram profile of antibiotic resistance. • For patients allergic to or intolerant of amoxicillin, alternatives include cephalosporins, macrolides, or quinolones. • First-generation cephalosporins, such as cephalexin and cefadroxil, have the disadvantage of poor coverage for *H influenzae* and are therefore inappropriate. • Cefaclor has inadequate activity against all β-lactamase–producing *M catarrhalis* and some, but not all, *H influenzae*. The high prevalence of serum sickness–like reactions makes it an unattractive candidate for treatment. • Other second-generation cephalosporins are cefuroxime axetil and cefprozil. These drugs have the advantage of twice-daily administration and significantly enhanced activity against β-lactamase–producing *H influenzae*, *M catarrhalis*, and *S aureus*. • Cefixime, ceftibuten, cefpodoxime axetil, and cefdinir are third-generation cephalosporins, which can be given orally once or twice daily. Both cefixime and ceftibuten have poor activity against *S pneumoniae* and are especially ineffective against penicillin-resistant strains. Neither of these drugs should be used for acute bacterial sinusitis. Cefpodoxime and cefdinir are suitable agents. • Acute sinusitis generally responds to treatment for 10 to 14 days. Some physicians continue treatment for 7 days after the patient is well to ensure complete eradication of the organism and prevent relapse. • A reasonable approach would be to start the patient on amoxicillin for 3 to 5 days and determine whether the signs and symptoms are improving. If the patients symptoms are improving, continue this treatment until the patient is well for 7 days (generally a 10- to 14-day course). If after 3 to 5 days the patient has not shown improvement, switch to a different antibiotic, such as high-dose amoxicillin-clavulanate or cefuroxime axetil.
American Academy of Pediatrics (AAP): **Clinical Practice Guideline: Management of Sinusitis**[27] **(2001)**	• Antibiotics are recommended for the management of acute bacterial sinusitis to achieve a more rapid clinical cure. • The principle bacterial pathogens in bacterial sinusitis are *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis.* • For children younger than 2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in degree of severity, who do not attend day care, and have not recently been treated with an antimicrobial, amoxicillin is recommended. • If the patient is allergic to amoxicillin, either cefdinir, cefuroxime, or

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	cefpodoxime can be used (only if the allergic reaction was not a type 1 hypersensitivity reaction). • In cases of serious allergic reactions, clarithromycin or azithromycin can be used in an effort to select an antimicrobial of an entirely different class. The Food and Drug Administration has not approved azithromycin for use in patients with sinusitis. • Alternative therapy in the penicillin-allergic patient who is known to be infected with a penicillin-resistant *S pneumoniae* is clindamycin. • If patients do not improve while receiving the usual dose of amoxicillin (45 mg/kg/d), have recently been treated with an antimicrobial, have an illness that is moderate or more severe, or attend day care, therapy should be initiated with high-dose amoxicillin-clavulanate (80–90 mg/kg/d of amoxicillin component, with 6.4 mg/kg/d of clavulanate in 2 divided doses). • Alternative therapies include cefdinir, cefuroxime, or cefpodoxime. A single dose of ceftriaxone, given either intravenously or intramuscularly, can be used in children with vomiting that precludes administration of oral antibiotics. Twenty-four hours later, when the child is clinically improved, an oral antibiotic is substituted to complete the therapy. • Recent pneumococcal surveillance studies indicate that resistance to trimethoprim-sulfamethoxazole and erythromycin-sulfisoxazole is substantial. Therefore, when patients fail to improve while receiving amoxicillin, neither trimethoprim-sulfamethoxazole nor erythromycin-sulfisoxazole are appropriate choices for antimicrobial therapy. • For patients who do not improve with a second course of antibiotics or who are acutely ill, there are 2 options. It is appropriate to consult an otolaryngologist for consideration of maxillary sinus aspiration to obtain a sample of sinus secretions for culture and sensitivity so that therapy can be adjusted precisely. Alternatively, the physician may prescribe intravenous cefotaxime or ceftriaxone (either in hospital or at home) and refer to an otolaryngologist only if the patient does not improve on intravenous antibiotics.
American College of Chest Physicians (ACCP): **Chronic Cough Due to Acute Bronchitis, ACCP Evidence-Based Clinical Practice Guidelines[33] (2006)**	• For patients with the putative diagnosis of acute bronchitis, routine treatment with antibiotics is not justified and should not be offered.
American College of Chest Physicians (ACCP): **Chronic Cough Due to Chronic Bronchitis, ACCP Evidence-Based Clinical Practice Guidelines[32] (2006)**	• In stable patients with chronic bronchitis, there is no role for long-term prophylactic therapy with antibiotics. • In patients with acute exacerbations of chronic bronchitis, the use of antibiotics is recommended; patients with severe exacerbations and those with more severe airflow obstruction at baseline are the most likely to benefit.

Global Initiative for Chronic Obstructive Lung Disease (GOLD): **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[31] (2010)**	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in COPD.
	• There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful.
	• Based on current available evidence, antibiotics should be given to:
	  o Patients with exacerbations of COPD with the following three cardinal symptoms: dyspnea, sputum volume, and sputum purulence.
	  o Patients with exacerbations of COPD with two of the cardinal

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	symptoms, if the increased purulence of sputum is one of the two symptoms. o Patients with a severe exacerbation of COPD that requires mechanical ventilation (invasive or noninvasive). • Antibiotic treatment in exacerbations of COPD: o Group A (mild exacerbation; no risk factors for poor outcome) ▪ Recommended oral treatment: β-lactam (penicillin, ampicillin, amoxicillin), tetracycline, or trimethoprim-sulfamethoxazole ▪ Alternative oral treatment: β-lactam/β-lactamase inhibitor, macrolides, second or third generation cephalosporin, or ketolides o Group B (moderate exacerbation with risk factor(s) for poor outcome) ▪ Recommended oral treatment: β-lactam/β-lactamase inhibitor ▪ Alternative oral treatment: fluoroquinolones (gemifloxacin, levofloxacin, moxifloxacin) ▪ Parenteral treatment: β-lactam/β-lactamase inhibitor, second or third generation cephalosporin, or fluoroquinolones (levofloxacin, moxifloxacin) o Group C (severe exacerbation with risk factors for *P. aeruginosa* infection) ▪ Recommended oral treatment: fluoroquinolones (ciprofloxacin, levofloxacin) ▪ Parenteral treatment: fluoroquinolones (ciprofloxacin, levofloxacin) or β-lactam with *P. aeruginosa* activity
Infectious Diseases Society of America (IDSA): **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age**[145] **(2011)**	Outpatient Treatment • Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia (CAP), because viral pathogens are responsible for the great majority of clinical disease. • Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate CAP suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*. • For patients allergic to amoxicillin, the following agents are considered alternative treatment options: o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil) o Levofloxacin (oral therapy) o Linezolid (oral therapy) • Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with CAP caused by atypical pathogens. Inpatient Treatment • Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with CAP when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *S. pneumoniae*. • Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-

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	level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. • Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *M. pneumoniae* and *C. pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *S. aureus*.

Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS): **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults[29] (2007)**	<u>Empirical Antimicrobial Therapy</u>
	• Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.
	• Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.
	• Outpatient treatment
	  o Previously healthy and no risk factors for drug-resistant *S. pneumoniae* (DRSP) infection:
	  ▪ Macrolide (azithromycin, clarithromycin, or erythromycin)
	  ▪ Doxycycline
	  o Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected); or other risks for DRSP infection:
	  ▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin)
	  ▪ β-lactam plus a macrolide (High-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide.)
	  o In regions with a high rate of infection with high-level macrolide-resistant *S. pneumoniae,* consider the use of alternative agents listed above for any patient, including those without comorbidities.
	• Inpatient, non-ICU treatment
	  o Respiratory fluoroquinolone
	  o β-lactam plus a macrolide (Preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients).
	• Inpatient, ICU treatment
	  o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended.)
	  o For *Pseudomonas* infection, use an antipneumococcal,

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	antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam). o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.
American College of Chest Physicians (ACCP): **Management of Community-Acquired Pneumonia in the Home: An American College of Chest Physicians Clinical Position Statement[30] (2005)**	• Antibiotic choice and route of administration are central to an appropriate in-home treatment plan. The oral route is recommended if the patient can tolerate it, and if the availability and activity of the agent are adequate. • Although treatment is facilitated if the etiologic agent is known (pathogen-directed treatment for CAP is provided in the IDSA guidelines), most outpatient treatment is empiric. • The use of a macrolide, doxycycline, or fluoroquinolone agent, as recommended both by the IDSA and the ATS guidelines, may be appropriate empiric outpatient treatment for low-risk patients (i.e., otherwise young healthy individuals). Alternatives to these agents in low-risk patients are amoxicillin/clavulanate and some second-generation cephalosporins (e.g., cefuroxime, cefpodoxime, or cefprozil). • A lack of response to treatment with macrolides and fluoroquinolones has been reported. Some authorities prefer to reserve the use of fluoroquinolones for older patients, patients who are allergic or intolerant to macrolides, patients who have recently received macrolide treatment, patients with comorbidities, patients with documented infections with highly resistant pneumococci, or patients with a lack of response to treatment with another agent. • The IDSA and ATS recommendations generally agree that a patient who is at high risk either because of complicated comorbidities or extensive prior antibiotic use may be a candidate for treatment with either a β-lactam/macrolide combination or a antipneumococcal fluoroquinolone. • Double therapy with either a β-lactam/macrolide combination or a β-lactam/antipneumococcal fluoroquinolone should be considered in patients who would normally be considered for ICU admission but have chosen to remain in the home.
American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA): **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia[18] (2005)**	• Select an initial empiric therapy based on the absence or presence of risk factors for multidrug-resistant (MDR) pathogens. These risk factors include prolonged duration of hospitalization (5 days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy. • Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins. • In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics. • Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors

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	for MDR pathogens, early onset, and any disease severity: o Ceftriaxone OR o Levofloxacin, moxifloxacin, ciprofloxacin OR o Ampicillin/sulbactam OR o Ertapenem • Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for MDR pathogens and all disease severity – combination antibiotic therapy is recommended as follows: o Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if MRSA risk factors are present or there is a high incidence locally.
Infectious Diseases Society of America (IDSA): **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children**[35] **(2010)**	Community-Acquired Infection in Adults: Mild to Moderate Severity • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*E. Coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. Community-Acquired Infection in Adults: High Severity • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *E. coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E. coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy.

Clinical Guideline	Recommendation(s)
	• Empiric use of agents effective against enterococci is recommended. • Use of agents effective against MRSA or yeast is not recommended in the absence of evidence of infection due to such organisms. Community-Acquired Infection in Pediatric Patients: • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected MRSA or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. Health Care-Associated Infection: • Therapy should be based on microbiologic results. To achieve empiric coverage, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. Cholecystitis and Cholangitis: • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.
Infectious Diseases Society of America (IDSA): **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus*[146] (2011)**	Skin and Soft-Tissue Infections (SSTIs) • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for

Clinical Guideline	Recommendation(s)
	community-acquired (CA) MRSA is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for CA-MRSA is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of CA-MRSA in outpatients with SSTI, oral antibiotic options include the following: clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and CA-MRSA is desired, options include the following: clindamycin alone or TMP-SMX or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of SSTIs is not recommended. • For hospitalized patients with complicated SSTIs, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for MRSA should be considered pending culture data. Options include the following: vancomycin intravenous (IV), linezolid oral (PO) or IV, daptomycin IV, telavancin IV, and clindamycin IV or PO. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to MRSA-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with cSSTIs, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin IV is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative. <u>MRSA Bacteremia and Infective Endocarditis (Native Valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin IV for at least 2 weeks is recommended. For complicated bacteremia, 4–6 weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, IV vancomycin or daptomycin for 6 weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>MRSA Bacteremia and Infective Endocarditis (Prosthetic Valve)</u> • IV vancomycin plus rifampin PO/IV for at least 6 weeks plus gentamicin IV for 2 weeks. • In children, vancomycin IV is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from 2 to 6 weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin IV may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not

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	related to an endovascular focus.
	• Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis.
	Management of MRSA Pneumonia
	• For hospitalized patients with severe community-acquired pneumonia, empirical therapy for MRSA is recommended pending sputum and/or blood culture results.
	• For health care–associated MRSA (HA-MRSA) or CA-MRSA pneumonia, IV vancomycin or linezolid PO/IV or clindamycin PO/IV, if the strain is susceptible, is recommended for 7–21 days, depending on the extent of infection.
	• In children, IV vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin IV can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative.
	Management of MRSA Bone and Joint Infections
	• Antibiotics available for parenteral administration include IV vancomycin and daptomycin.
	• Some antibiotic options with parenteral and oral routes of administration include the following: TMP-SMX in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.
	• A minimum 8-week course is recommended. Some experts suggest an additional 1–3 months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with TMP-SMX, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities.
	• For septic arthritis, refer to antibiotic choices for osteomyelitis. A 3 to 4-week course of therapy is suggested.
	Management of MRSA Infections of the CNS
	• Meningitis
	  o IV vancomycin for 2 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid or TMP-SMX.
	  o For CNS shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid (CSF) cultures are repeatedly negative.
	• Brain abscess, subdural empyema, spinal epidural abscess
	  o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and TMP-SMX.
	• Septic thrombosis of cavernous or dural venous sinus
	  o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and TMP-SMX.
	  o IV vancomycin is recommended in children.

Infectious Diseases Society of America (IDSA): **Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer[21] (2010)**	Initial Antibiotic Therapy
	• Oral route:
	  o For low-risk adults only; use ciprofloxacin plus amoxicillin-clavulanate
	• Monotherapy with vancomycin not indicated:
	  o Choose therapy with 1 of the following agents: cefepime or

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	ceftazidime, or imipenem or meropenem
	• Two drugs without vancomycin:
	  o Choose an aminoglycoside plus antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem
	• Vancomycin plus 1 or 2 antibiotics:
	  o Choose cefepime or ceftazidime plus vancomycin, with or without an aminoglycoside; carbapenem plus vancomycin, with or without an aminoglycoside; or antipseudomonal penicillin plus an aminoglycoside and vancomycin
	Modification of Therapy During the First Week of Treatment
	• Patient becomes afebrile in 3–5 days:
	  o Adjust therapy to the most appropriate drug(s). If no etiologic agent is identified and if the patient is at low risk initially, and oral antibiotic treatment was begun with no subsequent complications, continue use of the same drugs.
	  o If the patient was at low risk initially and therapy with intravenous drugs was begun with no subsequent complications, the regimen may be changed after 48 h to oral ciprofloxacin plus amoxicillin-clavulanate for adults or cefixime for children.
	  o If the patient is at high risk initially with no subsequent complications, continue use of the same intravenous drugs.
	• Persistent fever throughout the first 3–5 days:
	  o Reassess therapy on day 3. If there is no clinical worsening, continue use of the same antibiotics; stop vancomycin use if cultures do not yield organisms.
	  o If there is progressive disease, change antibiotics.
	  o If the patient is febrile after 5 days, consider adding an antifungal drug
	Antibiotic Prophylaxis for Afebrile Neutropenic Patients
	• Use of antibiotic prophylaxis is not routine because of emerging antibiotic resistance, except for the use of trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* pneumonitis.

Infectious Diseases Society of America (IDSA): **Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis[39] (2006)**	• Doxycycline, amoxicillin or cefuroxime axetil for 14 days is recommended for the treatment of adult patients with early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of specific neurologic manifestations (see Lyme meningitis, below) or advanced atrioventricular heart block. • Each of these antimicrobial agents has been shown to be highly effective for the treatment of erythema migrans and associated symptoms in prospective studies. • Doxycycline has the advantage of being effective for treatment of HGA (but not for babesiosis), which may occur simultaneously with early Lyme disease. • First-generation cephalosporins, such as cephalexin, are ineffective for treatment of Lyme disease and should not be used. • Ceftriaxone is not superior to oral agents and is more likely than the recommended orally administered antimicrobials to cause serious adverse effects. Therefore, ceftriaxone is not recommended for treatment of patients with early Lyme disease in the absence of neurologic involvement or advanced atrioventricular heart block.
Surgical Infection Prevention Guideline Writers Workgroup (SIPGWW): **Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the**	General Considerations • There is published evidence to support the use of many prophylactic antimicrobial regimens besides those included in this advisory statement or in existing guidelines.

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National Surgical Infection Prevention Project[37] (2004)	• Factors such as cost, half-life, safety, and antimicrobial resistance favor the use of older agents with a relatively narrow spectrum. • The use of newer, broad-spectrum drugs that are front-line therapeutic agents should be avoided in surgical prophylaxis to reduce emergence of bacterial strains that are resistant to these antimicrobials. <u>Gynecologic and Obstetrical Surgery</u> • For abdominal or vaginal hysterectomy, cefotetan is preferred, but reasonable alternatives are cefazolin and cefoxitin. In cases of β-lactam allergy, the workgroup recommends the use of one of the following regimens: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; metronidazole combined with gentamicin or ciprofloxacin; or clindamycin monotherapy. A single 750-mg dose of levofloxacin can be substituted for ciprofloxacin. • For cesarean section, a narrow-spectrum antimicrobial regimen similar to that recommended for hysterectomy provides adequate prophylaxis. <u>Orthopedic Total Joint (Hip and Knee) Arthroplasty</u> • The preferred antimicrobials for prophylaxis in patients undergoing hip or knee arthroplasty are cefazolin and cefuroxime. • Vancomycin or clindamycin may be used in patients with serious allergy or adverse reactions to β-lactams. <u>Cardiothoracic and Vascular Surgery</u> • The recommended antimicrobials for cardiothoracic and vascular operations include cefazolin or cefuroxime. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin is appropriate, and clindamycin may be an acceptable alternative. <u>Colorectal Surgery</u> • Antimicrobial prophylaxis for colorectal operations can consist of an orally administered antimicrobial bowel preparation, a preoperative parenteral antimicrobial, or the combination of both. • Recommended oral prophylaxis consists of neomycin plus erythromycin or neomycin plus metronidazole, initiated no more than 18–24 h before the operation, along with administration of a mechanical bowel preparation. • Cefotetan or cefoxitin are recommended for parenteral prophylaxis, and the combination of parenteral cefazolin and metronidazole is also recommended as an alternative. • For patients with confirmed allergy or adverse reaction to β-lactams, use of one of the following regimens is recommended: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; or metronidazole combined with gentamicin or ciprofloxacin. A single 750-mg dose of levofloxacin can be substituted for ciprofloxacin.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the cephalosporins are noted in Tables 5-6. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 5. FDA-Approved Indications for the Cephalosporins[1-13]

Indication	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefixime	Cefotaxime
Central Nervous System Infections								
Central nervous system infections								✔
Dermatological Infections								
Skin and skin-structure infections	✔ †‡	✔	✔	✔	✔	✔		✔
Genitourinary Infections								
Endometritis								✔
Genital infections			✔					
Gonorrhea							✔	✔
Pelvic cellulitis								✔
Pelvic inflammatory disease								✔
Urinary tract infections	✔ †	✔	✔			✔	✔	✔
Respiratory Infections								
Acute bronchitis	✔ ‡						✔	
Acute exacerbations of chronic bronchitis	✔ ‡			✔	✔		✔	
Otitis media	✔ †			✔			✔	
Pharyngitis and/or tonsillitis	✔ †‡	✔		✔	✔		✔	
Pneumonia	✔ †					✔		✔
Pneumonia (community-acquired)				✔	✔			
Sinusitis				✔				
Respiratory tract infections (lower)	✔ †		✔					✔
Respiratory tract infections (upper)			✔					
Miscellaneous Infections								
Bacteremia/Septicemia			✔					✔
Biliary tract infections			✔					
Bone and/or joint infections			✔					✔
Empiric therapy for febrile neutropenic patients						✔		
Endocarditis			✔					
Intra-abdominal infections						✔		✔
Perioperative prophylaxis			✔					✔

†Capsule formulation
‡Extended-release tablet formulation

Table 6. FDA-Approved Indications for the Cephalosporins (cont.)[1-13]

Indication	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Central Nervous System Infections								
Central nervous system infections				✔				
Meningitis				✔		✔	✔ §	
Dermatological Infections								
Impetigo							✔ ‡	
Skin and skin-structure infections	✔	✔	✔	✔		✔	✔ †§	✔
Genitourinary Infections								
Genitourinary infections								✔
Gonorrhea	✔					✔	✔ †§	
Gynecologic infections				✔		✔		
Urinary tract infections	✔			✔		✔	✔ †§	
Respiratory Infections								
Acute bronchitis		✔						
Acute exacerbations of chronic bronchitis	✔	✔			✔		✔ †	
Otitis media	✔	✔			✔	✔	✔ †‡	✔
Pharyngitis and/or tonsillitis	✔	✔			✔		✔ †‡	
Pneumonia				✔				
Pneumonia (community-acquired)	✔		✔					
Sinusitis	✔	✔					✔ †	
Respiratory tract infections (lower)				✔		✔	✔ §	✔
Respiratory tract infections (upper)								✔
Miscellaneous Infections								
Bone and/or joint infections				✔		✔	✔ §	✔
Intra-abdominal infections				✔		✔		
Lyme disease (early)							✔ †	
Perioperative prophylaxis						✔	✔ §	
Septicemia				✔		✔	✔ §	

§Injection formulation
‡Suspension formulation
†Tablet formulation

IV. Pharmacokinetics

The pharmacokinetic parameters of the cephalosporins are listed in Table 7.

Table 7. Pharmacokinetic Parameters of the Cephalosporins[1-13]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Cefaclor	Well absorbed	25	Not reported	Renal (50-80) Bile	0.5-1
Cefadroxil	Well absorbed	20	Not reported	Renal (85)	1.2-1.7
Cefazolin	N/A	80-86	Not metabolized	Renal (50-100)	1.5-2.5
Cefdinir	21-25	60-73	Not reported	Renal	1.7
Cefditoren	14-16	88	Intestinal wall Liver	Renal (16-22)	1.3-2
Cefepime	IM: Complete	16-20	Liver	Renal (70-99)	2
Cefixime	40-50	50-65	Not reported	Renal (50) Bile (5)	3-4
Cefotaxime	N/A	27-38	Liver	Renal (50-85)	0.8-1.4
Cefpodoxime	41-64	18-33	Not reported	Renal (29-33)	2-3
Cefprozil	89-95	35-45	Not reported	Renal (60-70)	1-2
Ceftaroline	N/A	20	Plasma	Renal (88) Feces (6)	2.6
Ceftazidime	IM: 91	5-17	Not metabolized	Renal (90-96)	1.6-2
Ceftibuten	80	65-77	Not reported	Renal (56)	1.53-2.5
Ceftriaxone	IM: 100 SC: 92	83-96	Intestinal wall	Renal (33-67) Bile (35-45)	5.8-8.7
Cefuroxime	37-52	50	Intestinal wall	Renal (66-100)	1.2-1.9
Cephalexin	Well absorbed	15-20	Not reported	Renal (>90)	0.9

V. Drug Interactions

Significant drug interactions with the cephalosporins are listed in Table 8.

Table 8. Significant Drug Interactions with the Cephalosporins[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Ceftriaxone	1	Calcium salts	Isolated neonatal deaths have been reported due to potential pulmonary and renal precipitation. Simultaneous administration of calcium-containing IV solutions and ceftriaxone in the same IV line should be avoided. A potential risk exists for calcium-ceftriaxone precipitation leading to gall bladder sludging, as well as precipitation, in the lungs and kidneys.
Cefdinir	2	Iron salts	Absorption of cefdinir is impaired when coadministered with iron salts.
Cephalosporins (cefdinir, cefditoren cefpodoxime)	2	Antacids	Plasma concentrations and antimicrobial effects of cephalosporins may be decreased by antacids.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the cephalosporins are listed in Tables 9-10.

Table 9. Adverse Drug Events (%) Reported with the Cephalosporins[1-13]

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefixime	Cefotaxime
Cardiovascular								
Arrhythmia	-	-	-	-	-	-	-	<1
Cardiac failure	-	-	-	<1	-	-	-	-
Chest pain	-	-	-	<1	-	-	-	-
Hypertension	-	-	-	<1	-	-	-	-
Myocardial infarction	-	-	-	≤1	-	-	-	-
Shock	-	-	-	<1	-	<1	-	-
Central Nervous System								
Agitation	<1	-	-	-	-	-	-	-
Coma	-	-	-	-	-	<1	-	-
Confusion	<1	-	-	-	-	<1	-	-
Dizziness	<1	-	-	<1	-	-	<2	-
Encephalopathy	-	-	-	-	-	<1	-	-
Fever	-	<1	✔	<1	-	1	<2	<1
Hallucinations	<1	-	-	-	-	<1	-	-
Headache	-	-	-	2	2-3	1	<2	<1
Hyperactivity	<1	-	-	-	-	-	-	-
Insomnia	<1	-	-	<1	-	-	-	-
Irritability	<1	-	-	-	-	-	-	-
Loss of consciousness	-	-	-	<1	-	-	-	-
Nervousness	<1	-	-	-	-	-	-	-
Paresthesias	<1	-	-	-	-	-	-	-
Seizures	<1	-	✔	-	-	<1	<2	-
Somnolence	<1	-	-	<1	-	-	-	-
Stupor	-	-	-	-	-	<1	-	-
Dermatological								
Angioedema	<1	<1	-	-	-	-	<2	-
Cutaneous moniliasis	-	-	-	<1	-	-	-	-
Erythema at injection site	-	-	-	-	-	1	-	-
Erythema multiforme	-	<1	-	<1	<1	-	<2	<1
Erythema nodosum	-	-	-	<1	-	-	-	-
Exfoliative dermatitis	-	-	-	<1	-	-	-	-

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefixime	Cefotaxime
Facial edema	-	-	-	<1	-	-	<2	-
Pruritus	<1	<1	✔	<1	-	1	-	1-10
Rash	1-2	<1	✔	≤3	<1	1-4	<2	1-10
Stevens-Johnson syndrome	<1	<1	✔	<1	<1	-	<2	<1
Toxic epidermal necrolysis	<1	-	-	<1	<1	-	<2	<1
Urticaria	<1	<1	-	-	-	<1	<2	<1
Gastrointestinal								
Abdominal pain	-	<1	✔	≤1	2	-	2-10	-
Anorexia	-	-	✔	<1	-	-	-	-
Bloody diarrhea	-	-	-	<1	-	-	-	-
Colitis	-	-	-	-	-	<1	-	1-10
Constipation	-	-	-	<1	-	-	-	-
Diarrhea	3	1-10	✔	8-15	11-15	≤3	16	1-10
Dyspepsia	-	<1	-	<1	1-2	-	2-10	-
Enterocolitis	-	-	-	<1	-	-	-	-
Flatulence	-	-	-	<1	-	-	2-10	-
GI bleed	-	-	-	<1	-	-	-	-
Hemorrhagic colitis	-	-	-	<1	-	-	-	-
Ileus	-	-	-	<1	-	-	-	-
Loose stools	-	-	-	-	-	-	2-10	-
Melena	-	-	-	<1	-	-	-	-
Nausea	<1	<1	✔	≤3	4-6	≤2	2-10	1-10
Oral candidiasis	-	-	✔	-	-	-	-	-
Oral moniliasis	-	-	-	-	-	<1	-	-
Peptic ulcer	-	-	-	<1	-	-	-	-
Pseudomonas colitis	<1	<1	✔	<1	<1	<1	-	<1
Stomatitis	-	-	-	<1	-	-	-	-
Stools abnormal	-	-	-	<1	-	-	-	-
Vomiting	<1	<1	✔	≤1	1	≤1	<2	1-10
Xerostomia	-	-	-	<1	-	-	-	-
Genitourinary								
Glycosuria	-	-	-	≤1	-	-	-	-
Hematuria	-	-	-	-	3	-	-	-
Interstitial nephritis	<1	-	-	-	-	-	-	<1
Leukorrhea	-	-	-	<1	<1	-	-	-
Microhematuria	-	-	-	≤1	-	-	-	-
Nephropathy	-	-	-	<1	-	-	-	-

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefixime	Cefotaxime
Proteinuria	-	-	-	≤1	-	-	-	-
Pyuria	-	-	-	-	2	-	-	-
Renal failure	-	-	✔	<1	<1	-	<2	-
Urine leukocytes increased	-	-	-	≤2	-	-	-	-
Urine pH increased	-	-	-	≤1	-	-	-	-
Urine specific gravity decreased	-	-	-	<1	-	-	-	-
Urine specific gravity increased	-	-	-	≤1	-	-	-	-
Vaginal moniliasis	-	-	-	<4	3-6	-	-	-
Vaginitis	2	<1	✔	≤1	-	<1	<2	<1
Hematologic								
Agranulocytosis	<1	<1	-	-	-	<1	-	-
Aplastic anemia	<1	-	-	-	-	-	-	-
Coagulation disorder	-	-	-	<1	-	-	-	-
Coagulation time increased	-	-	-	-	<1	-	-	-
Disseminated intravascular coagulation	-	-	-	<1	-	-	-	-
Eosinophilia	2	-	✔	1	-	2	<2	<1
Granulocytopenia	-	-	-	<1	-	-	-	-
Hematocrit decreased	-	-	-	-	2	<1	-	-
Hemoglobin decreased	-	-	-	<1	-	-	-	-
Hemolytic anemia	<1	-	-	<1	-	-	-	-
Leukocytosis	-	-	-	≤1	-	-	-	-
Leukopenia	-	-	✔	≤1	<1	<1	<2	-
Lymphocytes decreased	-	-	-	1	-	-	-	-
Lymphocytes increased	-	-	-	≤2	-	-	-	-
Monocytes increased	-	-	-	<1	-	-	-	-
Neutropenia	<1	<1	✔	-	-	<1	<2	<1
Pancytopenia	-	-	-	<1	-	-	-	-
PMN leukocytes changes	-	-	-	≤1	-	-	-	-
PT abnormal	-	-	-	-	-	1	-	-
PT prolonged	<1	-	-	-	-	-	<2	-
PTT abnormal	-	-	-	-	-	2	-	-
Thrombocythemia	-	-	-	-	<1	-	-	-
Thrombocytopenia	<1	<1	✔	<1	<1	<1	<2	<1
Thrombocytopenia purpura	-	-	-	<1	-	-	-	-
Thrombocytosis	-	-	✔	≤1	-	-	-	-
WBC decreased	-	-	-	<1	<1	-	-	-
WBC increased	-	-	-	<1	<1	-	-	-

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefixime	Cefotaxime
Hepatic								
Cholestasis	-	<1	-	<1	-	-	-	-
Hepatic failure	-	-	-	<1	-	-	-	-
Hepatitis	<1	-	✔	<1	-	-	<2	-
Jaundice	<1	-	-	<1	-	-	<2	-
Laboratory Test Abnormalities								
Albumin decreased	-	-	-	-	<1	-	-	-
Alkaline phosphatase increased	-	-	-	≤1	-	<1	-	-
Amylase increased	-	-	-	<1	-	-	-	-
Bicarbonate decreased	-	-	-	≤1	-	-	-	-
BUN increased	-	-	✔	<1	<1	<1	<2	<1
GGT increased	-	-	-	≤1	-	-	-	-
Hyperbilirubinemia	-	-	-	-	-	<1	<2	-
Hyperglycemia	-	-	-	≤1	1-2	-	-	-
Hyperkalemia	-	-	-	<1	<1	<1	-	-
Hyperphosphatemia	-	-	-	≤1	-	<1	-	-
Hypocalcemia	-	-	-	<1	<1	<1	-	-
Hyponatremia	-	-	-	-	<1	-	-	-
Hypophosphatemia	-	-	-	<1	-	3	-	-
Lactate dehydrogenase increased	-	-	-	≤1	-	-	-	-
Positive Coombs' test	-	-	-	-	<1	16	-	-
Serum creatinine increased	-	-	✔	-	-	<1	<2	<1
Transaminases increased	3	<1	✔	<1	-	2-3	<2	<1
Musculoskeletal								
Arthralgia	<1	<1	-	-	<1	-	-	-
Hyperkinesia	-	-	-	<1	-	-	-	-
Involuntary movement	-	-	-	<1	-	-	-	-
Myoclonus	-	-	-	-	-	<1	-	-
Rhabdomyolysis	-	-	-	<1	-	-	-	-
Weakness	-	-	-	<1	-	-	-	-
Respiratory								
Asthma	-	-	-	<1	<1	-	-	-
Eosinophilic pneumonia	-	-	-	<1	<1	-	-	-
Interstitial pneumonia	-	-	-	<1	<1	-	-	-
Pneumonia	-	-	-	<1	-	-	-	-
Respiratory failure	-	-	-	<1	-	-	-	-
Other								

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefixime	Cefotaxime
Allergic reaction	-	-	-	-	<1	-	-	-
Allergic vasculitis	-	-	-	<1	-	-	-	-
Anaphylaxis	<1	<1	✔	<1	-	<1	<2	<1
Bleeding tendency	-	-	-	<1	-	-	-	-
Candidiasis	-	-	-	-	-	-	<2	<1
Conjunctivitis	-	-	-	<1	-	-	-	-
Fungal infection	-	-	-	-	<1	-	-	-
Laryngeal edema	-	-	-	<1	-	-	-	-
Moniliasis	2	-	-	<1	-	-	-	-
Pain at injection site	-	-	✔	-	-	1	-	1-10
Phlebitis	-	-	✔	-	-	1	-	<1
Serum sickness-like reaction	<1	<1	-	<1	-	-	<2	-

✔ Percent not specified
- Event not reported

Table 10. Adverse Drug Events (%) Reported with the Cephalosporins (cont.)[1-13]

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Cardiovascular								
Bradycardia	-	-	<2	-	-	-	-	-
Chest pain	<1	-	-	-	-	-	-	-
Edema	-	-	-	-	-	<1	-	-
Hypotension	<1	-	-	-	-	-	-	-
Palpitation	-	-	<2	-	-	<1	-	-
Tachycardia	-	-	-	-	-	-	<1	-
Central Nervous System								
Agitation	-	-	-	-	<1	-	-	✔
Anxiety	<1	-	-	-	-	-	-	-
Confusion	-	<1	-	-	-	-	-	✔
Dizziness	<1	1	<2	<1	≤1	<1	-	✔
Encephalopathy	-	-	-	<1	-	-	-	-
Fatigue	<1	-	-	-	<1	-	-	✔
Fever	<1	<1	<2	<1	<1	<1	<1	-
Hallucinations	-	-	-	-	-	-	-	✔
Headache	1	<1	3-5	<1	≤3	<1	-	✔
Hyperactivity	-	<1	-	-	-	-	-	-
Insomnia	<1	<1	3-4	-	<1	-	-	-
Irritability	-	-	-	-	<1	-	-	-
Nightmares	<1	-	-	-	-	-	-	-

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Paresthesias	-	-	-	<1	<1	-	-	-
Psychosis	-	-	-	-	<1	-	-	-
Seizures	-	-	<2	-	-	<1	<1	-
Somnolence	-	<1	-	-	<1	-	-	-
Dermatological								
Allergic dermatitis	-	-	-	-	-	<1	-	-
Angioedema	-	<1	-	<1	-	-	<1	✔
Diaper rash	12	2	-	-	<1	-	3	-
Erythema multiforme	-	<1	-	<1	-	<1	<1	✔
Exanthema	-	-	-	-	-	<1	-	-
Flushing	<1	-	-	-	-	<1	-	-
Lyell's syndrome	-	-	-	-	-	<1	-	-
Pruritus	<1	-	3-4	<1	<1	<1	-	-
Rash	1	<1	3	<1	<1	2	<1	✔
Stevens-Johnson syndrome	-	<1	-	<1	<1	<1	<1	✔
Toxic epidermal necrolysis	-	-	-	<1	<1	<1	<1	✔
Urticaria	-	<1	<2	-	<1	<1	<1	✔
Gastrointestinal								
Abdominal pain	2	1	<2	-	1-2	<1	<1	✔
Anorexia	-	-	-	-	<1	-	-	-
Aphasia	-	-	-	-	<1	-	-	-
Appetite decrease	<1	-	-	-	-	-	-	-
C. difficile-associated diarrhea	-	-	<2	-	-	-	-	-
Colitis	-	-	-	-	-	<1	<1	-
Constipation	-	-	2	-	<1	-	-	-
Dehydration	-	-	-	-	<1	-	-	-
Diarrhea	7-15	3	5	1	3-4	3	4-11	✔
Dysgeusia	-	-	-	-	-	<1	-	-
Dyspepsia	-	-	-	-	≤2	<1	-	✔
Eructation	-	-	-	-	<1	-	-	-
Flatulence	<1	-	-	-	<1	<1	-	-
Gastritis	-	-	-	-	-	-	-	✔
GI bleed	-	-	-	-	-	-	<1	-
Glossitis	-	-	-	-	-	<1	-	-
Loose stools	-	-	-	-	≤2	-	-	-
Melena	-	-	-	-	<1	-	-	-
Nausea	4	4	4	<1	≤4	<1	3-7	✔

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Pseudomonas colitis	<1	<1	-	<1	<1	<1	<1	✔
Salivation decreased	<1	-	-	-	-	-	-	-
Stomatitis	-	-	-	-	-	<1	-	-
Taste alteration	<1	-	-	-	<1	-	-	-
Tongue swelling	-	-	-	-	-	-	<1	-
Vomiting	1-2	1	2	<1	1-2	<1	3-7	✔
Xerostomia	-	-	-	-	<1	-	-	-
Genitourinary								
Dysuria	-	-	-	-	<1	-	-	-
Genital moniliasis	-	-	-	-	-	-	-	✔
Genital pruritus	-	2	-	-	-	-	-	✔
Glycosuria	-	-	-	-	-	<1	-	-
Hematuria	-	-	-	-	<1	<1	-	-
Interstitial nephritis	-	-	-	-	-	-	<1	✔
Nephrolithiasis	-	-	-	-	-	<1	-	-
Oliguria	-	-	-	-	-	<1	-	-
Purpuric nephritis	<1	-	-	-	-	-	-	-
Renal dysfunction	-	-	-	-	-	-	<1	-
Renal failure	-	-	<2	-	-	-	-	-
Renal precipitations	-	-	-	-	-	<1	-	-
Urinary casts	-	-	-	-	-	<1	-	-
Vaginal candidiasis	<1	-	-	-	-	-	-	-
Vaginal discharge	-	-	-	-	-	-	-	✔
Vaginal infection	3	-	-	-	-	-	-	-
Vaginitis	-	1-10	-	<1	<1	<1	≤5	✔
Hematologic								
Agranulocytosis	-	-	-	-	-	<1	-	-
Anemia	-	-	<2	-	-	<1	-	-
Basophilia	-	-	-	-	-	<1	-	-
Eosinophilia	-	<1	<2	<1	3	6	7	✔
Hematocrit decreased	-	-	-	-	-	-	10	-
Hemoglobin decreased	-	-	-	-	1-2	-	10	-
Hemolytic anemia	-	-	-	<1	-	<1	<1	✔
Leukocytosis	-	-	-	-	-	<1	-	-
Leukopenia	-	<1	-	<1	<1	2	<1	-
Lymphocytosis	-	-	-	-	-	<1	-	-
Lymphopenia	-	-	-	-	-	<1	-	-

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Monocytosis	-	-	-	-	-	<1	-	-
Neutropenia	-	-	<2	-	-	<1	<1	✔
Pancytopenia	-	-	-	-	-	-	<1	-
PT decreased	-	-	-	-	-	<1	-	-
PT prolonged	-	-	-	-	-	<1	<1	-
Thrombocytopenia	-	<1	<2	-	<1	<1	<1	✔
Thrombocytosis	-	-	-	<1	≤1	5	-	-
Hepatic								
Cholestasis	-	-	-	-	-	-	<1	-
Hepatitis	-	-	<2	-	-	-	<1	✔
Jaundice	-	<1	-	<1	<1	<1	<1	✔
Laboratory Test Abnormalities								
Alkaline phosphatase increased	-	-	-	-	<1	<1	2	-
BUN increased	-	<1	-	<1	2-4	1	<1	-
Hyperbilirubinemia	-	-	-	<1	≤1	<1	<1	-
Hyperglycemia	-	-	<2	-	-	-	-	-
Hyperkalemia	-	-	<2	-	-	-	-	-
Hypokalemia	-	-	2	-	-	-	-	-
Lactate dehydrogenase increased	-	-	-	-	-	-	1	-
Positive Coombs' test	-	-	11	-	-	-	<1	-
Serum creatinine increased	-	<1	-	<1	<1	<1	<1	-
Transaminases increased	-	2	2	<1	≤1	3	2-4	✔
Musculoskeletal								
Arthralgia	-	<1	-	-	-	-	-	✔
Arthritis	-	-	-	-	-	-	-	✔
Asterixis	-	-	-	<1	-	-	-	-
Hyperkinesia	-	-	-	-	<1	-	-	-
Joint disorder	-	-	-	-	-	-	-	✔
Malaise	<1	-	-	-	-	-	-	-
Myoclonus	-	-	-	<1	-	-	-	-
Neuromuscular excitability	-	-	-	<1	-	-	-	-
Rigors	-	-	-	-	<1	-	-	-
Weakness	<1	-	-	-	-	-	-	-
Respiratory								
Allergic pneumonitis	-	-	-	-	-	<1	-	-
Bronchospasm	-	-	-	-	-	<1	-	-
Cough	<1	-	-	-	-	-	-	-

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Dyspnea	-	-	-	-	<1	-	<1	-
Nasal congestion	-	-	-	-	<1	-	-	-
Pulmonary precipitations	-	-	-	-	-	<1	-	-
Stridor	-	-	-	-	<1	-	-	-
Other								
Allergic reactions	-	-	-	-	-	-	-	✔
Anaphylaxis	<1	<1	<2	<1	-	<1	<1	✔
Biliary lithiasis	-	-	-	-	-	<1	-	-
Candidiasis	-	-	-	<1	-	-	-	-
Chills	-	-	-	-	-	<1	-	-
Diaphoresis	-	-	-	-	-	<1	-	-
Epistaxis	<1	-	-	-	-	<1	-	-
Eye itching	<1	-	-	-	-	-	-	-
Fungal infection	<1	-	-	-	-	-	-	-
Gallbladder sludge	-	-	-	-	-	<1	-	-
Gallstones	-	-	-	-	-	<1	-	-
Hypersensitivity reactions	-	-	<2	2	-	-	<1	-
Moniliasis	-	-	-	-	<1	<1	-	-
Pain at injection site	-	-	-	1	-	1	<1	-
Pancreatitis	-	-	-	-	-	<1	-	-
Phlebitis	-	-	2	<1	-	<1	-	-
Serum sickness-like reaction	-	<1	-	-	<	<1	-	-
Superinfection	-	1-10	-	-	-	-	-	-
Thrombophlebitis	-	-	-	-	-	-	2	-
Tinnitus	<1	-	-	-	-	-	-	-

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the cephalosporins are listed in Table 11.

Table 11. Usual Dosing Regimens for the Cephalosporins[1-13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Cefaclor	Acute Bronchitis: Tablet (ER 12H): 500 mg every 12 hours for 7 days Acute Exacerbations of Chronic Bronchitis: Tablet (ER 12H): 500 mg every 12 hours for 7 days Otitis Media: Capsule (IR): 250 mg every 8 hours Pharyngitis and/or Tonsillitis: Capsule (IR): 250 mg every 8 hours Tablet (ER 12H): 375 mg every 12 hours for 10 days Respiratory Tract Infections (Lower): Capsule (IR): 250 mg every 8 hours Skin and Skin-Structure Infections: Capsule (IR): 250 mg every 8 hours Tablet (ER 12H): 375 mg every 12 hours for 7 to 10 days Urinary Tract Infections: Capsule (IR): 250 mg every 8 hours	Otitis Media: Capsule (IR): 20 mg/kg/day in divided doses every 8 hours Pharyngitis and/or Tonsillitis: Capsule (IR): 20 mg/kg/day in divided doses every 8 hours Respiratory Tract Infections (Lower): Capsule (IR): 20 mg/kg/day in divided doses every 8 hours Skin and Skin-Structure Infections: Capsule (IR): 20 mg/kg/day in divided doses every 8 hours Urinary Tract Infections: Capsule (IR): 20 mg/kg/day in divided doses every 8 hours	Capsule (IR): 250 mg 500 mg Tablet (ER 12H): 500 mg
Cefadroxil	Pharyngitis and/or Tonsillitis: Capsule/suspension/tablet: 1 g per day in single (QD) or divided doses (BID) for 10 days Skin and Skin-Structure Infections (Uncomplicated): Capsule/suspension/tablet: 1 g per day in single (QD) or divided doses (BID) Urinary Tract Infections: Capsule/suspension/tablet: Complicated: 2 g per day in divided doses (BID)	Impetigo: Capsule/suspension/tablet: 30 mg/kg/day in a single dose or in equally divided doses every 12 hours Pharyngitis and/or Tonsillitis: Capsule/suspension/tablet: 30 mg/kg/day in a single dose or in equally divided doses every 12 hours for 10 days Skin and Skin-Structure Infections (Uncomplicated): Capsule/suspension/tablet:	Capsule: 500 mg Suspension: 250 mg/5 ml 500 mg/5 ml Tablet: 1 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Uncomplicated: 1 or 2 g per day in single (QD) or divided doses (BID)	30 mg/kg/day in equally divided doses every 12 hours Urinary Tract Infections: Capsule/suspension/tablet: 30 mg/kg/day in divided doses every 12 hours	
Cefazolin	Life-Threatening Infections: 1 to 1.5 g every 6 hours Mild Infections: 250 mg to 500 mg every 8 hours Moderate to Severe Infections: 500 mg to 1 g every 6 to 8 hours Perioperative Prophylaxis: Preoperative: 1 g IV/IM administered 30 minutes to 1 hour prior to the start of surgery Intraoperative: 500 mg to 1 g IV/IM during surgery Postoperative: 500 mg to 1 g IV/IM every 6 to 8 hours for 24 hours Pneumonia: 500 mg every 12 hours Urinary Tract Infections (Uncomplicated): 1 g every 12 hours	Mild to Moderately Severe Infections: >1 month of age: 25 to 50 mg/kg divided into 3 or 4 equal doses Severe Infections: >1 month of age: 25 to 100 mg/kg divided into 3 or 4 equal doses	Injection: 500 mg 1 g 1 g/50 ml 10 g 20 g
Cefdinir	Acute Exacerbations of Chronic Bronchitis: Capsule: 300 mg every 12 hours for 5 to 10 days or 600 mg every 24 hours for 10 days Pharyngitis and/or Tonsillitis: Capsule: 300 mg every 12 hours for 5 to 10 days or 600 mg every 24 hours for 10 days Pneumonia (Community-Acquired): Capsule: 300 mg every 12 hours for 10 days Sinusitis: Capsule: 300 mg every 12 hours or 600 mg every 24 hours for 10 days Skin and Skin-Structure	Otitis Media: 6 months to 12 years of age: Suspension: 7 mg/kg every 12 hours for 5 to 10 days or 14 mg/kg every 24 hours for 10 days Pharyngitis and/or Tonsillitis: 6 months to 12 years of age: Suspension: 7 mg/kg every 12 hours for 5 to 10 days or 14 mg/kg every 24 hours for 10 days Sinusitis: 6 months to 12 years of age: Suspension: 7 mg/kg every 12 hours or 14 mg/kg every 24 hours for 10 days Skin and Skin-Structure Infections (Uncomplicated):	Capsule: 300 mg Suspension: 125 mg/5 ml 250 mg/5 ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Infections: Capsule: 300 mg every 12 hours or 600 mg every 24 hours for 10 days	6 months to 12 years of age: Suspension: 7 mg/kg every 12 hours for 10 days	
Cefditoren	Acute Exacerbations of Chronic Bronchitis: 400 mg twice daily for 10 days Pharyngitis and/or Tonsillitis: 200 mg twice daily for 10 days Pneumonia (Community-Acquired): 400 mg twice daily for 14 days Skin and Skin-Structure Infections (Uncomplicated): 200 mg twice daily for 10 days	Acute Exacerbations of Chronic Bronchitis: ≥12 years of age: 400 mg twice daily for 10 days Pharyngitis and/or Tonsillitis: ≥12 years of age: 200 mg twice daily for 10 days Pneumonia (Community-Acquired): ≥12 years of age: 400 mg twice daily for 14 days Skin and Skin-Structure Infections (Uncomplicated): ≥12 years of age: 200 mg twice daily for 10 days	Tablet: 200 mg 400 mg
Cefepime	Empiric Therapy for Febrile Neutropenic Patients: 2 g IV every 8 hours for 7 days or until resolution of neutropenia Intra-Abdominal Infections (Complicated): 2 g IV every 12 hours for 7 to 10 days Pneumonia (Moderate to Severe): 1 to 2 g IV every 12 hours for 10 days Skin and Skin-Structure Infections (Moderate to Severe): 2 g IV every 12 hours for 10 days Urinary Tract Infections: Mild to moderate: 0.5 to 1 g IM/IV every 12 hours for 7 to 10 days Severe: 2 g IV every 12 hours for 10 days	Empiric Therapy for Febrile Neutropenic Patients: 2 months to 16 years of age: 50 mg/kg IV every 8 hours for 7 days or until resolution of neutropenia Pneumonia: 2 months to 16 years of age: 50 mg/kg IV every 12 hours for 10 days Skin and Skin-Structure Infections (Uncomplicated): 2 months to 16 years of age: 50 mg/kg IV every 12 hours for 10 days Urinary Tract Infections 2 months to 16 years of age: Mild to moderate: 50 mg/kg IV every 12 hours for 7 to 10 days Severe: 50 mg/kg IV every 12 hours for 10 days	Injection: 1 g 1 g/50 ml 2 g 2 g/50ml 2 g/100 ml
Cefixime	Gonorrhea (Uncomplicated): Tablet: 400 mg as a single dose Unspecified Infections: Tablet: 400 mg once daily or 200 mg every 12 hours	Unspecified Infections: 6 months to 12 years of age: Suspension: 8 mg/kg once daily or 4 mg/kg every 12 hours	Suspension: 100 mg/5 ml 200 mg/5 ml Tablet: 400 mg
Cefotaxime	Gonococcal Infections:	Unspecified Infections:	Injection:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Rectal: 0.5 g IM as a single dose in females and 1 g IM as a single dose in males Urethritis/cervicitis: 0.5 g IM as a single dose Life-Threatening Infections: 2 g IV every 4 hours Moderate to Severe Infections: 1 to 2 g IM/IV every 8 hours Perioperative Prophylaxis: 1 g IM/IV as a single dose administered 30 to 90 minutes prior to the start of surgery Uncomplicated Infections: 1 g IM/IV every 12 hours	0-1 week of age: 50 mg/kg IV per dose every 12 hours 1-4 weeks of age: 50 mg/kg IV per dose every 8 hours 1 month to 12 years of age: <50 kg: 50 to 180 mg/kg IM/IV divided into 4 to 6 equal doses ≥50 kg: usual adult dosage	500 mg 1 g 2 g 10 g 20 g
Cefpodoxime	Acute Exacerbations of Chronic Bronchitis: Tablet: 200 mg every 12 hours for 10 days Gonococcal Infections: Suspension/tablet: Rectal: 200 mg as a single dose in females Uncomplicated gonorrhea: 200 mg as a single dose Pharyngitis and/or Tonsillitis: Suspension/tablet: 100 mg every 12 hours for 5 to 10 days Pneumonia (Community-Acquired): Suspension/tablet: 200 mg every 12 hours for 14 days Sinusitis: Suspension/tablet: 200 mg every 12 hours for 10 days Skin and Skin-Structure Infections: Suspension/tablet: 400 mg every 12 hours for 7 to 14 days Urinary Tract Infections (Uncomplicated): Suspension/tablet: 100 mg every 12 hours for 7 days	Acute Exacerbations of Chronic Bronchitis: ≥12 years of age: Tablet: 200 mg every 12 hours for 10 days Gonococcal Infections: ≥12 years of age: Suspension/tablet: Rectal: 200 mg as a single dose in females Uncomplicated gonorrhea: 200 mg as a single dose Otitis Media: 2 months to 12 years of age: Suspension: 5 mg/kg every 12 hours for 5 days Pharyngitis and/or Tonsillitis: 2 months to 12 years of age: Suspension: 5 mg/kg every 12 hours for 5 to 10 days ≥12 years of age: Suspension/tablet: 100 mg every 12 hours for 5 to 10 days Pneumonia (Community-Acquired): ≥12 years of age: Suspension/tablet: 200 mg every 12 hours for 14 days Sinusitis:	Suspension: 50 mg/5 ml 100 mg/5 ml Tablet: 100 mg 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		2 months to 12 years of age: Suspension: 5 mg/kg every 12 hours for 10 days ≥12 years of age: Suspension/tablet: 200 mg every 12 hours for 10 days Skin and Skin-Structure Infections: ≥12 years of age: Suspension/tablet: 400 mg every 12 hours for 7 to 14 days Urinary Tract Infections (Uncomplicated): ≥12 years of age: Suspension/tablet: 100 mg every 12 hours for 7 days	
Cefprozil	Acute Bronchitis: Suspension/tablet: 500 mg every 12 hours for 10 days Acute Exacerbations of Chronic Bronchitis: Suspension/tablet: 500 mg every 12 hours for 10 days Pharyngitis and/or Tonsillitis: Suspension/tablet: 500 mg every 24 hours for 10 days Sinusitis: Suspension/tablet: 250 to 500 mg every 12 hours for 10 days Skin and Skin-Structure Infections: Suspension/tablet: 250 to 500 mg every 12 hours or 500 mg every 24 hours for 10 days	Acute Bronchitis: ≥13 years of age: Suspension/tablet: 500 mg every 12 hours for 10 days Acute Exacerbations of Chronic Bronchitis: ≥13 years of age: Suspension/tablet: 500 mg every 12 hours for 10 days Otitis Media: 6 months to 12 years of age: Suspension/tablet: 15 mg/kg every 12 hours for 10 days Pharyngitis and/or Tonsillitis: 2 to 12 years of age: Suspension/tablet: 7.5 mg/kg every 12 hours for 10 days ≥13 years of age: Suspension/tablet: 500 mg every 24 hours for 10 days Sinusitis: 6 months to 12 years of age: Suspension/tablet: 7.5 mg/kg to 15 mg/kg every 12 hours for 10 days ≥13 years of age: Suspension/tablet: 250 to 500 mg every 12 hours for 10 days Skin and Skin-Structure Infections:	Suspension: 125 mg/5 ml 250 mg/5 ml Tablet: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		2 to 12 years of age: Suspension/tablet: 20 mg/kg every 24 hours for 10 days ≥13 years of age: Suspension/tablet: 250 to 500 mg every 12 hours or 500 mg every 24 hours for 10 days	
Ceftaroline	Pneumonia (Community-Acquired): 600 mg every 12 hours for 5 to 7 days Skin and Skin-Structure Infections: 600 mg every 12 hours for 5 to 14 days	Safety and efficacy in children have not been established.	Injection: 400 mg 600 mg
Ceftazidime	Bone and Joint Infections: 2 g IV every 12 hours Gynecologic Infections (Serious): 2 g IV every 8 hours Intra-Abdominal Infections (Serious): 2 g IV every 8 hours Life-Threatening Infections (Very Severe): 2 g IV every 8 hours Lung Infections (Cystic Fibrosis Patients): 30 to 50 mg/kg IV every 8 hours Meningitis: 2 g IV every 8 hours Pneumonia (Uncomplicated): 500 mg to 1 g IM/IV every 8 hours Skin and Skin-Structure Infections (Mild): 500 mg to 1 g IM/IV every 8 hours Urinary Tract Infections Uncomplicated: 250 mg IM/IV every 12 hours Complicated: 500 mg IM/IV every 8 to 12 hours	Unspecified Infections: 0 to 4 weeks of age: 30 mg/kg IV every 12 hours 1 month to 12 years of age: 30 to 50 mg/kg IV every 8 hours	Injection: 500 mg/vial 1 g 1 g/50 ml 2 g 2 g/50 ml 6 g
Ceftibuten	Acute Exacerbations of Chronic Bronchitis:	Otitis Media: ≥6 months of age:	Capsule: 400 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Capsule/suspension: 400 mg once daily for 10 days Otitis Media: Capsule/suspension: 400 mg once daily for 10 days Pharyngitis and/or Tonsillitis: Capsule/suspension: 400 mg once daily for 10 days	Capsule/suspension: 9 mg/kg once daily for 10 days. Patients weighing>45 kg should receive 400 mg once daily. Pharyngitis and/or Tonsillitis: ≥6 months of age: Capsule/suspension: 9 mg/kg once daily for 10 days. Patients weighing>45 kg should receive 400 mg once daily.	Suspension: 90 mg/5 ml 180 mg/5 ml
Ceftriaxone	Gonococcal Infections (Uncomplicated): 250 mg IM as a single dose Preoperative Prophylaxis: 1 g IV as a single dose administered 30 minutes to 2 hours prior to surgery Unspecified Infections: 1 to 2 g IM/IV once daily	Meningitis: 100 mg/kg once daily or divided every 12 hours Otitis Media: 50 mg/kg IM as a single dose Skin and Skin-Structure Infections: 50 to 75 mg/kg once daily or in equally divided doses twice daily Unspecified Infections: 50 to 75 mg/kg/day given in divided doses every 12 hours	Injection: 250 mg 500 mg 1 g 1 g/50 ml 2 g 2 g/50 ml 10 g
Cefuroxime	Acute Bronchitis: Tablet: 250 to 500 mg twice daily for 5 to 10 days Acute Exacerbations of Chronic Bronchitis: Tablet: 250 to 500 mg twice daily for 10 days Bone and Joint Infections: Injection: 1.5 g IM/IV every 8 hours Gonococcal Infections: Disseminated: Injection: 750 mg IM/IV every 8 hours Uncomplicated: Injection: 1.5 g IM as a single dose Tablet: 1,000 mg as a single dose Life-Threatening Infections: Injection: 1.5 g IM/IV every 6 hours	Acute Bronchitis: ≥13 years of age Tablet: 250 to 500 mg twice daily for 5 to 10 days Acute Exacerbations of Chronic Bronchitis: ≥13 years of age: Tablet: 250 to 500 mg twice daily for 10 days Bone and Joint Infections: >3 months of age: Injection: 150 mg/kg/day IM/IV divided every 8 hours Gonorrhea (Uncomplicated): ≥13 years of age: Tablet: 1,000 mg as a single dose Impetigo: 3 months to 12 years of age: Suspension: 30 mg/kg/day divided twice daily for 10 days Lyme Disease (Early): ≥13 years of age: Tablet: 500 mg twice daily for	Injection: 750 mg 750 mg/50 ml 1.5 g 1.5 g/50 ml 7.5 g Suspension: 125 mg/5 ml 250 mg/5 ml Tablet: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Lyme Disease (Early): Tablet: 500 mg twice daily for 20 days Meningitis: Injection: 3 g IM/IV every 8 hours Perioperative Prophylaxis: Injection: Clean-contaminated procedures: 1.5 g IV one hour prior to surgery, then 750 mg IM/IV every 8 hours when the surgery is prolonged Open heart surgery: 1.5 g IV every 12 hours for a total of 6 g Pharyngitis and/or Tonsillitis: Tablet: 250 mg twice daily for 10 days Pneumonia (Uncomplicated): Injection: 750 mg IM/IV every 8 hours Severe or Complicated Infections (Unspecified): Injection: 1.5 g IM/IV every 8 hours Sinusitis: ≥13 years of age Tablet: 250 mg twice daily for 10 days Skin and Skin-Structure Infections (Uncomplicated): Injection: 750 mg IM/IV every 8 hours Tablet: 250 to 500 mg twice daily for 10 days Unspecified Infections: Injection: 750 mg to 1.5 g IM/IV every 8 hours for 5 to 10 days Urinary Tract Infections (Uncomplicated): Injection: 750 mg IM/IV every 8 hours Tablet: 250 mg twice daily for 7 to 10 days	20 days Meningitis: >3 months of age: Injection: 200 to 240 mg/kg/day IV divided every 6 to 8 hours Otitis Media: 3 months to 12 years of age: Suspension: 30 mg/kg/day divided twice daily for 10 days Tablet: 250 mg twice daily for 10 days Pharyngitis and/or Tonsillitis: 3 months to 12 years of age: Suspension: 20 mg/kg/day divided twice daily for 10 days ≥13 years of age: Tablet: 250 mg twice daily for 10 days Sinusitis: 3 months to 12 years of age: Suspension: 30 mg/kg/day divided twice daily for 10 days Tablet: 250 mg twice daily for 10 days ≥13 years of age Tablet: 250 mg twice daily for 10 days Skin and Skin-Structure Infections (Uncomplicated): ≥13 years of age: Tablet: 250 to 500 mg twice daily for 10 days Unspecified Infections: >3 months of age: Injection: 50 to 100 mg/kg/day IM/IV divided every 6 to 8 hours Urinary Tract Infections (Uncomplicated): ≥13 years of age: Tablet: 250 mg twice daily for 7 to 10 days	

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Cephalexin	Cystitis (Uncomplicated): Capsule/suspension/tablet: 500 mg every 12 hours for 7 to 14 days Skin and Skin-Structure Infections: Capsule/suspension/tablet: 500 mg every 12 hours Streptococcal Pharyngitis: Capsule/suspension/tablet: 500 mg every 12 hours Unspecified Infections: Capsule/suspension/tablet: 250 mg every 6 hours	Otitis Media: Capsule/suspension/tablet: 75 to 100 mg/kg/day in 4 divided doses Streptococcal Pharyngitis: >1 year of age: Capsule/suspension/tablet: 25 to 50 mg/kg/day every 12 hours for at least 10 days Unspecified Infections: Capsule/suspension/tablet: 25 to 50 mg/kg/day in divided doses	Capsule: 250 mg 500 mg 750 mg Suspension: 125 mg/5 ml 250 mg/5 ml Tablet: 250 mg 500 mg

ER 12H=extended-release, 12 hour; IR=immediate-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cephalosporins are summarized in Table 12.

Table 12. Comparative Clinical Trials with the Cephalosporins

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Ballantyne et al.[98] (1985) Cefaclor 250 mg PO TID vs cefadroxil 1,000 mg PO QD	OL, RCT Patients aged 6 to 80 years with skin and soft-tissue infections	N=200 10 days	Primary: Clinical and bacteriological efficacy, medication adherence	Primary: There was no statistically significant difference in terms of clinical efficacy for patients treated with cefadroxil and cefaclor (91% vs 95%, respectively; P=0.41). Medication adherence was greater in patients treated with cefadroxil compared to patients treated with cefaclor based on the percentage of patients returning unused capsules (2% vs 77%, respectively).
Ballantyne et al.[100] (1980) Cefadroxil 500 mg PO BID vs cefadroxil 1,000 mg PO QD vs cefadroxil 1,000 mg PO BID vs cephalexin 500 mg PO QID	DB, MC (2 trials) Patients with skin and soft-tissue infections	N=224 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: In study A, improvement in clinical and bacteriologic evaluations were reported in patients treated with cefadroxil and cephalexin (100% vs 91%, respectively). In study B, improvement in clinical and bacteriologic evaluations was reported in patients treated with both cefadroxil doses and cephalexin (98% vs 97% vs 98%, respectively). Based on the studies in this meta-analysis, overall clinical and bacteriologic response to cefadroxil and cephalexin were both reported as 96%. Secondary: No significant drug-related adverse events were reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
In study A, participants received either cefadroxil 1,000 mg BID or cephalexin; in study B, participants received either cefadroxil 500 mg BID or 1,000 mg QD or cephalexin.				
Bucko et al.[104] (2002) Cefadroxil 500 mg PO BID vs cefditoren 200 mg PO BID vs cefditoren 400 mg PO BID vs cefuroxime 250 mg PO BID In study A, participants received cefditoren 200 mg or	DB, MC, PG (2 trials) Patients with uncomplicated skin and skin structure infections	N=1,685 10 days	Primary: Clinical evaluation, microbiologic evaluation Secondary: Adverse events	Primary: Clinical cure rates were reported as 85%, 83%, 88% and 85% for patients treated with cefditoren 200 mg, cefditoren 400 mg, cefuroxime, and cefadroxil, respectively. At 7 to 14 days after treatment completion, eradication rates were higher in patients treated with cefuroxime compared to patients treated with cefditoren 200 mg in study 1 (P=0.043). At 7 to 14 days after treatment completion, eradication rates were higher for cefditoren 400 mg compared to patients treated with cefadroxil in study 2 (P=0.018). Secondary: A higher rate of drug-related adverse events were reported for patients treated with cefditoren 400 mg compared to all other treatment groups (P<0.05 for each comparison). The most common adverse events were mild cases of diarrhea, nausea, and headache.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cefuroxime; in study B, participants received cefditoren 400 mg or cefadroxil.				
Gooch et al.[105] (1991) Cefadroxil 500 mg PO BID vs cefuroxime 250 mg PO BID vs cephalexin 500 mg PO BID	DB, MC, PG, RCT Patients with mild to moderate infections of the skin or skin structures	N=330 10 days	Primary: Clinical and bacteriological response Secondary: Adverse events	Primary: A positive clinical outcome was achieved in 97%, 89%, and 94% of patients treated with cefuroxime, cephalexin, and cefadroxil, respectively (P=0.047, cefuroxime vs cephalexin). A positive bacteriological outcome was achieved in 96%, 85% and 93% of patients treated with cefuroxime, cephalexin, and cefadroxil, respectively (P=0.026, cefuroxime vs cephalexin). Secondary: There was no significant difference in reported drug-related gastrointestinal adverse events by patients treated with cefuroxime, cephalexin, or cefadroxil (9.3% vs 7.2% vs 9.8%, respectively).
Leder et al.[96] (1998) Cefazolin 2 g IV BID	OS, PRO Patients 18 to 90 years of age with moderate to severe cellulitis using home-based therapy	N=57 3 to 13 days	Primary: Clinical efficacy Secondary: Adverse events	Primary: Clinical cure was reported in 93% of patients treated with cefazolin; failure occurred in 3 patients. Secondary: Cefazolin was well tolerated.
Tack et al.[101] (1997) Cefdinir 7 mg/kg PO BID vs cephalexin 10	DB, MC, RCT Patients aged 6 months to 12 years diagnosed with uncomplicated mild to moderate skin or skin-structure infec-tion warranting	N=231 10 days	Primary: Clinical cure rate, microbiologic eradication rate Secondary: Adverse events	Primary: Clinical cure rates were reported as 98.3% and 93.8% in patients treated with cefdinir and cephalexin, respectively (P=0.056). Microbiologic eradication rates were reported as 99.4% and 97.4% in patients treated with cefdinir and cephalexin, respectively (P=0.14). Secondary: Drug-related adverse events were reported in 16% and 11% of patients treated with cefdinir and cephalexin, respectively (P=0.11). The most

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg PO QID	systemic anti-microbial therapy and/or drainage			common side effect was diarrhea.
Giordano et al.[123] (2006) Cefdinir 300 mg twice daily vs cephalexin 250 mg four times daily	RCT, SB, MC Patients ≥13 years of age with mild to moderate uncomplicated skin and skin structure infections (uSSSI)	N=391 24 days	Primary: Clinical cure rates in clinically evaluable patients at the test-of-cure (TOC) visit Secondary: Bacteriological cure, pathogen eradication rates, adverse events	Primary: There were no statistically significant differences between the treatment groups in clinical response. At the TOC visit, the clinical cure rate was 89% for cefdinir and 89% for cephalexin in clinically evaluable patients (95% CI, -6.7 to 7.3) and 88% among clinically and bacteriologically evaluable patients (95% CI, –7.7% to 7.5%). In the intent-to-treat analysis, cure rates were 83% for cefdinir and82% for cephalexin. Clinical cure rates for infections caused by methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) *Staphylococcus aureus* were 93% and 92%, respectively for cefdinir compared to 91% and 90%, respectively for cephalexin (P>0.999 comparing treatment groups for MSSA; P>0.999 comparing treatments for MRSA). Secondary: The treatment groups were similar based on patient bacteriological cure rates in the clinically and bacteriologically evaluable patients: 87% for cefdinir and 86% for cephalexin in patients with any isolate at baseline. The usefulness questionnaire demonstrated that cefdinir was more highly rated in the mean composite score (87.4 vs 83.6, P=0.04), with the difference primarily due to the respondents' preference for the convenience of taking the study medication (mean score 93.5 vs 74.1 for cephalexin, P<0.001). There were no statistically significant differences between treatment groups in the patient self-assessment questionnaire, the healthcare resource utilization questionnaire, and patient diary data. Both study drugs were well tolerated. The most common treatment-related adverse events were diarrhea, (10% cefdinir, 4% cephalexin, P=0.017), nausea (3% and 6%, respectively, P=0.203), and vaginal mycosis (3% and 6% of females, respectively, P=0.500).
Gentry et al.[51]	OL, PRO, RCT	N=112	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1991) Cefepime 2 g IV BID vs ceftazidime 2 g IV every 8 hours	Patients with skin or wound infections and complicated nosocomial urinary tract infections	4 to 28 days	Clinical efficacy, microbiologic eradication Secondary: Adverse events	Relative to skin/skin structure and wound infections, clinical efficacy was reported as 90% and 96% of patients treated with cefepime and ceftazidime, respectively (P=0.68); microbiologic eradication rate was reported as 94% and 95%, respectively. Relative to nosocomial urinary tract infections, clinical efficacy was reported as 84% and 88% of patients treated with cefepime and ceftazidime, respectively (P=1.0); microbiologic eradication was reported as 100% and 95%, respectively. Secondary: Both treatments were well tolerated. Increased serum creatinine and diarrhea were the only mild adverse events reported.
Gentry et al.[102] (1989) Cefotaxime 2 g IV TID and 1 placebo tablet PO BID vs ciprofloxacin 750 mg PO BID and placebo IV over 30 minutes TID	DB, MC, PRO, RCT Patients with culture-confirmed skin or skin structure infections requiring hospitalization	N=461 4 to 34 days	Primary: Clinical response, bacteriologic response, overall response rate Secondary: Adverse events	Primary: For patients treated with cefotaxime, clinical response was reported as 74%, 20%, and 6% characterized as resolution, improvement, and failure, respectively. For patients treated with ciprofloxacin, clinical response was reported as 81%, 16%, and 3% characterized as resolution, improvement, and failure, respectively. For all comparisons, P=NS. Bacteriologic eradication was reported as 87% and 84% for patients treated with ciprofloxacin and cefotaxime, respectively (P=0.0123). Overall efficacy rate was reported as 76% and 75% for patients treated with ciprofloxacin and cefotaxime, respectively. Overall failure rate was higher in patients treated with cefotaxime compared to ciprofloxacin (8% vs 2%, respectively; P=0.0081). Secondary: There was no statistically significant difference in adverse events for treatment groups. However, there was a higher incidence of metabolic and nutritional systems-related events in patients treated with ciprofloxacin ($0.01<P<0.05$).
Stevens et al.[99] (1993) Cefpodoxime 400	DB, MC, PC, RCT Patients aged ≥12 years with acute	N=371 7 to 10 days	Primary: Clinical evaluations, microbiologic	Primary: Both cefpodoxime and cefaclor were highly effective for the treatment of single-site skin or skin-structure infections (99% pathogen eradication and 86% cure rate).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg PO BID vs cefaclor 500 mg PO TID	single-site skin or skin-structure infections		evaluations	There were no significant differences in the failure rate with cefpodoxime and cefaclor. Both active drug regimens were well tolerated.
Corey et al.[130] (2010) Ceftaroline 600 mg every 12 hours for 5 to 14 days vs vancomycin 1 g plus aztreonam 1 g every 12 hours for 5 to 14 days	RCT, MC, DB, AC Patients ≥18 years of age with complicated skin and skin structure infections (cSSSIs) who required ≥5 days of parenteral antibacterial therapy	N=702 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (8–15 days after administration of the last dose of study medication) in the clinically evaluable (CE) and modified intent-to-treat (MITT) populations Secondary: Microbiological success rate, safety	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the CE (91.1% vs 93.3%; 95% CI, -6.6 to 2.1) and MITT (86.6% vs 85.6%; 95% CI, -4.2 to 6.2) populations, respectively. Secondary: The clinical cure rate for MRSA cSSSIs was 95.1% for ceftaroline and 95.2% for vancomycin plus aztreonam. Similar cure rates were found in patients with MSSA (91.3% and 94.6%), as well as in the patients from whom Gram-negative pathogens were isolated. The microbiological success rate was similar for ceftaroline and vancomycin overall, and for MRSA. Among the ME patients, the baseline pathogen(s) was eradicated or presumed eradicated at similar rates in both the ME and mMITT populations (91.8% and 86.3% for ceftaroline; 92.5% and 83.7% for vancomycin plus aztreonam; 95% CI, -5.7 to 4.4 and 95% CI, -3.4 to 8.9, respectively). The incidence of AEs was similar in both study groups. The majority of AEs were mild in severity and similar in type among study groups. Diarrhea occurred in 3.4% vs 3.2% of patients in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively.
Wilcox et al.[131] (2010) Ceftaroline 600 mg every 12 hours for 5 to 14 days	RCT, MC, DB, AC Patients ≥18 years of age with complicated skin and skin structure infections (cSSSIs)	N=694 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (8–15 days after administration of the last dose of	Primary: Cure rates at TOC were comparable in both treatment groups across all study populations. In the CE population, cure rates were 92.2% and 92.1% for ceftaroline and vancomycin plus aztreonam, respectively (95% CI, -4.4 to 4.5). In the MITT population, clinical cure rates for ceftaroline and vancomycin plus aztreonam were similar (85.1% vs 85.5%, respectively; 95% CI, -5.8 to 5.0).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs vancomycin 1 g plus aztreonam 1 g every 12 hours for 5 to 14 days	who required ≥5 days of parenteral antibacterial therapy		study medication) in the clinically evaluable (CE) and modified intent-to-treat (MITT) populations Secondary: Microbiological success rate, safety	Secondary: In patients with MRSA isolated at baseline, cure rates were 91.4% and 93.3% for ceftaroline and vancomycin plus aztreonam, respectively. Similar cure rates were found in patients with MSSA (94.4% in both groups) as well as in the patients from whom a Gram-negative pathogen was isolated. Baseline pathogens were eradicated or presumed eradicated at similar rates in both the ME and mMITT populations among Gram-positive and a limited number of Gram-negative pathogens (92.9% and 86.6% for ceftaroline; 95.0% and 88.4% for vancomycin plus aztreonam; 95% CI, -6.9 to 2.5 and 95% CI, -7.5 to 3.9, respectively). There were no microbiological reinfections or recurrences at the LFU visit in either treatment group. The incidence of AEs was similar in both study groups. The majority of AEs were mild in severity and similar in type among study groups. Diarrhea occurred in 6.5% vs 4.4% in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively. AEs considered related to the study drug and occurring in ≥3% of patients were diarrhea and pruritus.
Corey et al.[137] (2010) Ceftaroline 600 mg every 12 hours for 5 to 14 days vs vancomycin 1 g plus aztreonam 1 g every 12 hours for 5 to 14 days	Pooled analysis (2 trials) Patients ≥18 years of age with complicated skin and skin structure infections (cSSSIs) who required ≥5 days of parenteral antibacterial therapy	N=1,378 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (8–15 days after administration of the last dose of study medication) in the clinically evaluable (CE) and modified intent-to-treat (MITT) populations Secondary:	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the CE (91.6% vs 92.7%) and MITT (85.9% vs 85.5%) populations, respectively. Secondary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in patients infected with MRSA (93.4% vs 94.3%). The efficacy of ceftaroline and vancomycin plus aztreonam against polymicrobial and monomicrobial infections was similar. Clinical relapse at the late follow-up visit was noted in 1.1% of patients in the ceftaroline group compared with 0.9% of patients in the vancomycin plus aztreonam group (CE).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Microbiological success rate, safety	Favorable microbiological response (ME) was observed in 92.3% of patients in the ceftaroline group compared to 93.7% of patients in the vancomycin plus aztreonam group (95% CI, -4.8% to 2.0%). Incidences of treatment-emergent AEs were similar among the treatment groups. Diarrhea occurred in 4.9% of patients in the ceftaroline group and in 3.8% of patients in the vancomycin plus aztreonam group (MITT population). AEs considered to be related to study drug in ≥3% of patients were pruritus, nausea, and diarrhea.
Gentry et al.[103] (1989) Ceftazidime 2 g IV every 8 hours vs ciprofloxacin 200 mg IV every 12 hours, then ciprofloxacin 750 mg PO every 12 hours	PRO, RCT Patients with serious infections of the skin and skin structures caused by gram-negative organisms	N=51 19 to 25 days	Primary: Cure rate Secondary: Adverse events	Primary: Cure rate was reported as 75% and 58% in patients treated with ciprofloxacin and ceftazidime, respectively (P<0.05). Bacteriologic cure was reported as 78% and 72% in patients treated with ciprofloxacin and ceftazidime, respectively. Superinfection was reported as 28% and 11% in patients treated with ciprofloxacin and ceftazidime, respectively (0.01<P<0.05). Secondary: Adverse events were reported in 6% and 5% of patients treated with ciprofloxacin and ceftazidime, respectively.
Eron et al.[97] (1983) Ceftriaxone 1 g IV BID vs ceftriaxone 2 g IV QD (children ≤15 years old: 50 mg/kg/day in divided doses)	PRO, XO Patients aged 2 to 86 years old with bone or soft tissue infection	N=100 3 to 56 days	Primary: Clinical response Secondary: Adverse events	Primary: Positive clinical response was reported as 91% of patients for both the twice-daily and once-daily treatment groups; 89% vs 94%, respectively. Failed therapy was reported in 9 patients caused by resistance, superinfection, or an underlying disease. Intravenous therapy was continued in 41 patients in the outpatient setting. Secondary: Ten percent of patients treated with ceftriaxone reported diarrhea; of these, 3 patients required discontinuation of treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Khawcharoenporn et al.[140] (2010) Cephalexin 500 mg 4 times per day vs trimethoprim-sulfamethoxazole 1 double strength tablet twice daily vs clindamycin 300 mg 4 times per day	RETRO Patients ≥18 years of age with cellulitis	N=405 Variable duration	Primary: Treatment success rate, compliance, safety	Primary: The overall treatment success rate with trimethoprim-sulfamethoxazole was significantly higher than the success rate with cephalexin (91% vs 74%; P<0.001). Clindamycin success rate was higher than that of cephalexin but did not reach statistical significance (85% vs 74%; P=0.22). The success rates of trimethoprim-sulfamethoxazole and clindamycin were comparable. The treatment success rate with trimethoprim-sulfamethoxazole was significantly more successful than cephalexin in patients who were male (P=0.001), were Pacific Islanders (P=0.001), had diabetes mellitus (P=0.001), were obese (P=0.002), had positive cultures for MRSA (P=0.01), and were cigarette smokers (P=0.04). The treatment success rate with clindamycin was higher than with cephalexin in patients who had MRSA infections (P<0.01), had moderately severe cellulitis (P<0.03), and were obese (P<0.04). Methicillin-resistant *S. aureus* was recovered in 62% of positive culture specimens. Compliance and adverse drug reaction rates were not significantly different among patients who received these 3 antibiotics. Factors associated with treatment failure included therapy with an antibiotic that was not active against community-associated MRSA (P<0.001) and severity of cellulitis (P<0.001).
Genitourinary Infections				
Leigh et al.[44] (2000) Cefaclor 250 PO TID vs cefdinir 100 mg	DB, MC, PG, RCT Patients ≥13 years of age with uncomplicated urinary tract infections	N=383 5 days	Primary: Clinical and microbiologic efficacy Secondary: Adverse events	Primary: A greater number of pathogens were resistant to treatment with cefaclor compared to cefdinir (6.7% vs 3.7%, respectively; P<0.003). Isolates of *E coli* were more resistant to treatment with cefaclor compared to cefdinir (5.1% vs 2%, respectively; P<0.007). At 5 to 9 days post treatment, patients treated with cefdinir and cefaclor reported statistically equivalent clinical (91.3% vs 93.0%, respectively; P=0.539) and microbiologic (84.7% vs 79.7%, respectively; P=0.184)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PO BID				response rates. Secondary: Drug-related side effects were greater in patients treated with cefdinir compared to patients treated with cefaclor (20.2% vs 13.0%, respectively; P=0.025).
Christenson et al.[45] (1991) Cefaclor 250 mg PO TID vs cefprozil 500 mg PO QD	OL, RCT Patients ≥18 years of age with acute, uncomplicated urinary tract infection	N=98 10 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: Clinical efficacy was reported as 87% and 78% in patients treated with cefprozil and cefaclor, respectively (P=NS). Bacteriologic eradication was reported as 80% and 82% in patients treated with cefprozil and cefaclor, respectively (P=NS). Secondary: Leukopenia and nausea was more commonly reported by patients treated with cefprozil though the difference is not statistically significant (P=0.08 and P=0.07, respectively).
Bolding et al.[46] (1980) Cefadroxil 1,000 mg PO BID vs cephalexin 500 PO mg QID	DB, RCT Females aged 18 to 63 years with urinary tract infections	N=26 10 to 13 days	Primary: Clinical cure rate Secondary: Adverse event	Primary: Clinical cure rates were achieved in 100% and 92% of patients treated with cephalexin and cefadroxil, respectively, within 5 to 9 days. One patient treated with cefadroxil was not cured due to an *E coli* urinary tract infection. Secondary: One patient taking cefadroxil reported side effects of nausea and vomiting which may be associated with concurrent therapy with propoxyphene-acetaminophen. Patients treated with cefadroxil reported less vaginal itching or irritation compared to patients treated with cephalexin.
Madsen et al.[47] (1981) Cefazolin 1,000 mg IM every 8 hours vs cefotaxime 500 mg	2 RCT Males aged 83 to 89 years with complicated urinary tract infections	N=91 7 to 10 days	Primary: Clinical cure rate Secondary: Adverse events	Primary: One week after treatment completion, clinical cure rates were reported as 71% and 60% in patients treated with cefotaxime and cefazolin, respectively. One week after treatment completion, clinical cure rates were reported as 64% and 59% in patients treated with cefotaxime 500 mg and 1,000 mg, respectively. No significant difference was found between the two groups. Secondary:

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IM every 8 hours vs cefotaxime 1,000 mg IM every 8 hours In study A, participants received 1 or 2 doses of cefotaxime; in study B, participants received cefotaxime 500 mg or cefazolin.				Both treatments were well-tolerated by study participants.
Sanchez-Ramos et al.[48] (1995) Cefazolin 2 g IV every 8 hours vs ceftriaxone 1 g IV once daily and normal saline IV every 8 hours from the ceftriaxone dose for 2 doses	DB, MC, RCT Pregnant patients with acute pyelo-nephritis confirmed by chill symptoms, costovertebral angle tenderness, urinalysis showing bacteria and white cells	N=178 48 hours to 10 days	Primary: Febrile morbidity, length of hospital stay, treatment failures	Primary: There was no statistically significant difference between patients treated with ceftriaxone and cefazolin in terms of mean length of hospital stay (3.7 vs 4.0 days, respectively), temperature (101 vs 101.4 degrees F, respectively), length of fever (1 vs 1.3 days, respectively), or required intravenous doses (8.1 vs 8.8. doses, respectively; P=NS). Treatment failures were reported in 5.7% and 3.3% of patients treated with cefazolin and ceftriaxone, respectively (P=0.71).
Iversen et al.[49] (1981) Cefazolin 1 g IM	PRO, RCT Males aged 38 to 91 years with urinary	N=58 5 to 10 days	Primary: Therapeutic efficacy	Primary: After 1 day of treatment, 97% of patients reported negative urine cultures for both treatment groups; one week after treatment completion, 62% and 63% of cultures were negative for patients treated with cefuroxime and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
every 8 hours vs cefuroxime 0.75 g IM every 8 hours	tract infections associated with benign hyperplasia of the prostate, carcinoma of the prostate or bladder, or urethral stricture		Secondary: Adverse events	cefazolin, respectively; P=NS. Secondary: Minor pain at the injection site was the most common adverse event reported. Both treatments were well tolerated.
Newton et al.[50] (1993) Cefepime 2 g IM (or by a 30-minute IV infusion) BID vs cefotaxime 2 g IM (or by a 30-minute IV infusion) TID	MC, OL, RCT Female patients ≥18 years of age with acute obstetric and gynecological infections	N=131 2 to 10 days	Primary: Clinical response, microbiological eradication, overall response Secondary: Adverse events	Primary: Satisfactory clinical response was reported in 85% and 83% of patients treated with cefepime and cefotaxime, respectively (P=0.802); microbiological eradication was reported as 81% and 86%, respectively (P=0.379). Overall response of effective, partially effective, and ineffective was reported as 77%, 13% and 11%, respectively, in patients treated with cefepime; for patients treated with cefotaxime, percentages of 75%, 19%, and 6%, respectively, were reported for overall response. Secondary: Drug-related adverse events were reported in 6% and 1% of patients treated with cefepime and cefotaxime, respectively (P=0.342). Drug-related discontinuation of therapy was reported in 5 and 1 patient(s) treated with cefepime and cefotaxime, respectively (P=0.476).
Gentry et al.[51] (1991) Cefepime 2 g IV BID vs ceftazidime 2 g IV every 8 hours	OL, PRO, RCT Patients with skin or wound infections and complicated nosocomial urinary tract infections	N=112 4 to 28 days	Primary: Clinical efficacy, microbiologic eradication Secondary: Adverse events	Primary: Relative to skin/skin structure and wound infections, clinical efficacy was reported as 90% and 96% of patients treated with cefepime and ceftazidime, respectively (P=0.68); microbiologic eradication rate was reported as 94% and 95%, respectively. Relative to nosocomial urinary tract infections, clinical efficacy was reported as 84% and 88% of patients treated with cefepime and ceftazidime, respectively (P=1.0); microbiologic eradication was reported as 100% and 95%, respectively. Secondary: Both treatments were well tolerated. Increased serum creatinine and diarrhea were the only mild adverse events reported.
Arrieta et al.[57] (2001) Cefepime 50	MA Patients aged 1 month to 18 years	N=521 (5 trials) 2 to 14 days	Primary: Clinical efficacy, microbiologic efficacy	Primary: In study A, clinical efficacy was reported as 98% and 96% for patients treated with cefepime and ceftazidime, respectively; at treatment completion, bacteriologic eradication was reported as 96% and 94%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg IV every 8 hours vs cefepime 50 mg/kg IV every 12 hours vs ceftazidime 50 mg/kg IV every 8 hours vs cefotaxime 30 mg/kg IV every 6 hours In studies A and B, participants received either cefepime or ceftazidime every 8 hours. In study C, D, and E, participants received either cefepime every 8 hours or cefepime every 12 hours or cefotaxime.	with serious urinary tract infections, including pyelonephritis		Secondary: Adverse events	respectively. In study B, clinical efficacy was reported as 97% and 100% for patients treated with cefepime and ceftazidime, respectively; bacteriologic eradication was reported as 95% and 92%, respectively. In studies C, D, and E, overall clinical efficacy was reported as 91% and 100% in patients treated with cefepime and cefotaxime, respectively; bacteriologic eradication was reported as 94% and 100%, respectively. Secondary: In study A, there was no statistically significant difference in drug-related adverse events between treatment groups (P=0.40). In studies D and E, both treatment regimens were well tolerated. The most commonly reported adverse events were gastrointestinal in nature.
Ho et al.[52] (2001) Cefixime 200 mg	OL, PRO, RCT Patients ≥18 years of age with	N=45 10 to 14 days	Primary: Clinical efficacy rate, bacteriological	Primary: There was no statistically significant difference in rates of clinical efficacy (78.3% vs, 77.3%, P=0.9) and bacteriological eradication (52.2% and 63.6%, P=0.08) for patients taking ceftibuten and cefixime, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PO BID vs ceftibuten 200 mg PO BID	complicated urinary tract infections		eradication rate Secondary: Adverse events	 Secondary: Adverse events were minimal for both treatment groups. Patients treated with ceftibuten reported diarrhea and increased transaminase serum levels; patients treated with cefixime reported skin rash and increased transaminase serum levels.
Aplasca de los Reyes et al.[56] (2001) Cefixime 400 mg PO for 1 dose vs ciprofloxacin 500 mg PO for 1 dose	PRO, RCT, SB Female sex workers >16 years of age with gonorrhea in Cebu and Manila, Philippines with documented high-level ciprofloxacin resistance	N=101 1 day	Primary: Treatment failure	Primary: After 28 days post-treatment, treatment failure was reported as 3.8% and 32.3% in patients treated with cefixime and ciprofloxacin, respectively (P<0.01).
Tripi et al.[53] (1985) Cefotaxime 0.5 to 1 g IV/IM BID vs ceftizoxime 0.5 to 1 g IV/IM BID	DB, PRO, RCT Patients with acute or chronic urinary tract infections	N=80 10 days	Primary: Therapeutic efficacy Secondary: Adverse events	Primary: For either the ceftizoxime and cefotaxime study groups, clinical responses classified as excellent, good, or fair were reported as 90%, 7.5% and 2.5%, respectively. Secondary: Excellent tolerance rates to ceftizoxime and cefotaxime were reported as 100.0% and 97.5%, respectively.
Mårild et al.[133] (2009) Ceftibuten 9 mg/kg oral suspension once daily for 10 days vs	RCT, OL, MC Patients 1 month to 12 years of age with a first-time febrile urinary tract infection (UTI)	N=547 14 to 20 days	Primary: Bacteriological and clinical outcomes	Primary: In the intention-to-treat population, the bacteriological elimination rates in the ceftibuten and TMP-SMX groups were 91% and 95%, respectively (P=NS). In the per protocol population, the bacteriological elimination rates in the ceftibuten and TMP-SMX groups were 91% and 97%, respectively (P<0.01). In the intention-to-treat population, the clinical cure rates among patients

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sulfamethoxazole-trimethoprim 3 mg + 15 mg/kg oral suspension twice daily for 10 days (TMP-SMX)				treated with ceftibuten and TMP-SMX were 93% and 83%, respectively (P=0.008). In the per protocol population, the clinical cure rates were 93% and 90%, respectively (P=NS). Adverse events were reported by 3% of the patients in the ceftibuten group and by 5% in the TMP-SMX group (P=NS). Gastrointestinal symptoms were reported most frequently. There were no serious adverse events reported.
Goldstein et al.[54] (1991) Ceftizoxime 250 mg IM for 1 dose vs ceftriaxone 250 mg IM for 1 dose	DB, PRO Adult heterosexual male inmates with documented uncomplicated urethral gonorrhea	N=204 1 day	Primary: Clinical cure Secondary: Adverse events	Primary: At 7 to 10 days post-treatment, all patients in both treatment groups achieved cure (100%). Secondary: No adverse events were reported.
Cooper et al.[55] (1992) Cefuroxime 125 mg PO BID vs cephradine 500 mg PO BID	PRO, RCT Patients ≥17 years of age with dysuria or frequency and diagnosed urinary tract infection	N=113 7 days	Primary: Clinical cure, bacteriological cure Secondary: Adverse events	Primary: At 7 days post-treatment, clinical cure rates were reported as 56% and 81% in patients treated with cephradine and cefuroxime, respectively (P<0.05). Bacteriological cure at 1 week post-treatment and 5 weeks post-treatment were reported as 97% and 96%, respectively, for both study groups (P>0.05). Secondary: Fourteen percent and 6% of patients treated with cephradine and cefuroxime, respectively, reported adverse events; patients receiving cefuroxime reported a higher incidence of increased frequency of bowel movements (35% vs 17.5%, respectively; P<0.05).
Ziogos et al.[129] (2010) Cefuroxime 1.5 g IV as a single dose	RCT Women scheduled for cesarean delivery	N=176 30 days	Primary: Development of an infection	Primary: Postoperative infections developed in 5.9% of patients receiving cefuroxime and 8.8% of patients receiving ampicillin-sulbactam (P=0.6). In univariate analyses 6 or more vaginal examinations prior to the

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vs ampicillin-sulbactam 3 g IV as a single dose				operation (P=0.004), membrane rupture for more than 6 hours (P=0.08) and blood loss greater than 500 ml (P=0.018) were associated with developing a postoperative surgical site infection (SSI). In logistic regression having 6 or more vaginal examinations was the most significant risk factor for a postoperative SSI (OR 6.8; 95% CI, 1.4 to 33.4; P0.019). Regular prenatal follow-up was associated with a protective effect (OR 0.04; 95% CI, 0.005-0.36; P=0.004). Patients that developed an infection had a lengthier hospital stay (median of 5 vs. 4 days; P<0.001). All patients with an infection responded well to subsequent antibiotics. No adverse drug reactions were reported.
Respiratory Infections—Upper Respiratory Tract				
Randolph et al.[58] (1988) Cefaclor 20 mg/kg PO TID vs cefadroxil 30 mg/kg PO QD	PRO, RCT Patients aged between 3 and 21 years with clinical signs and symptoms of acute group A β-hemolytic streptococcal pharyngitis	N=250 10 days	Primary: Clinical evaluation, microbiologic evaluations Secondary: Adverse event	Primary: On day 14 (P=0.020) and days 21 to 28 (P=0.043), a greater number of patients treated with cefadroxil had good therapeutic response to therapy compared to patients treated with cefaclor. Patients treated with cefadroxil had a lower failure or clinical recurrence compared to patients treated with cefaclor (4.6% vs 22.1%, respectively). Secondary: No significant drug-related adverse event reported.
Piippo et al.[59] (1991) Cefaclor 40 mg/kg/day PO divided BID vs cefixime 8 mg/kg/day PO	DB, PG, RCT Pediatric patients aged 6 months to 12 years with acute otitis media	N=345 7 days	Primary: Clinical cure Secondary: Adverse events	Primary: At days 10-12, clinical cure was reported in 93.5% and 90.5% of patients treated with cefixime and cefaclor, respectively (P=0.081). At days 28 to 35, clinical cure was reported in 90.1% and 86.6% of patients treated with cefixime and cefaclor, respectively (P=0.12). Secondary: Adverse events were reported in 17.9% and 10.6% of patients treated with cefixime and cefaclor, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
divided BID				
Gehanno et al.[60] (1990) Cefaclor 500 mg PO TID vs cefpodoxime 200 mg PO BID	DB, MC, PC, PRO, RCT Adult outpatients with acute sinusitis	N=236 Mean days 9.9	Primary: Clinical cure, overall clinical efficacy (cure and improvement), bacteriological eradication Secondary: Adverse events	Primary: At the end of the treatment, clinical cure was reported as 84% and 68% of patients treated with cefpodoxime and cefaclor, respectively (P=0.01). Overall clinical efficacy was reported as 95% and 93% of patients treated with cefpodoxime and cefaclor, respectively (P=NS). Bacteriological eradication was reported as 95% and 91% in patients treated with cefpodoxime and cefaclor, respectively (P=NS). Secondary: Possible drug-related adverse events were reported in 9 and 10 patients treated with cefpodoxime and cefaclor, respectively.
MacLoughlin et al.[61] (1996) Cefaclor suspension 40 mg/kg/day PO divided TID vs cefpodoxime suspension 10 mg/kg/day PO divided BID	MC, OL, RCT Pediatric patients aged 1 month to 11 years with acute otitis media	N=167 5 days	Primary: Clinical efficacy Secondary: Adverse events	Primary: Clinical success was reported as 93.6% and 91.6% of patients treated with cefpodoxime and cefaclor, respectively (*P* >0.05); at study day 30, clinical recurrence was reported as 99% and 94%, respectively (P>0.05). Secondary: Patients were able to tolerate both cefpodoxime and cefaclor (99% vs 94%, respectively; P>0.05).
Blumer et al.[62] (1995) Cefaclor 40 mg/kg/day PO in three divided doses (maximum 1 g/day) vs	MC, RCT, SB Pediatric patients aged 3 months to 17 years with acute otitis media	N=154 10 days	Primary: Clinical cure Secondary: Adverse events	Primary: At 1 to 3 days post-treatment, clinical cure was reported in 89% and 88% of patients treated with ceftibuten and cefaclor, respectively (P=NS). At 2 to 4 weeks post-treatment, clinical cure was reported in 88% and 82% of patients treated with ceftibuten and cefaclor, respectively (P=NS). Secondary: Mild to moderate drug-related adverse events were reported in 8% and 14% of patients treated with ceftibuten and cefaclor, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ceftibuten 9 mg/kg/day PO for 1 dose (maximum 400 mg/day)				
McCarty[76] (1994) Cefaclor 20 mg/kg/day PO divided TID (maximum 750 mg/day) vs cefprozil 20 mg/kg/day PO QD (maximum 500 mg/day) vs cefprozil 15 mg/kg PO divided BID (maximum 500 mg/day) vs erythromycin 30 mg/kg/day PO divided QID (maximum 1,600 mg/day) vs	4 MC, RCT Patients ≥2 years of age with mild to moderate group A β-hemolytic streptococcal tonsillitis and pharyngitis	N=1,186 10 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: In study A, clinical efficacy was reported as 89% and 74% in patients treated with cefprozil and penicillin, respectively; bacteriologic eradication was reported as 89% and 67%, respectively. In study B, clinical efficacy was reported as 93% and 90% in patients treated with cefprozil and cefaclor, respectively; bacteriologic eradication was reported as 95% and 94%, respectively. In study C, clinical efficacy was reported as 94% and 88% for patients treated with cefprozil compared to penicillin. In study D, clinical and bacteriologic efficacy was reported as 95% for both treatment groups (i.e., cefprozil and erythromycin). Secondary: There was no statistically significant difference in patients treated with any of the treatments in regards to adverse events. Adverse events were mostly gastrointestinal.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
penicillin 46 mg/kg/day PO divided TID (maximum 780 mg/day) In study A, participants received either cefprozil QD or penicillin. In study B, participants received either cefprozil QD or cefaclor. In study C, participants received either cefprozil BID or penicillin. In study D, participants received either cefprozil QD or erythromycin.				
Milatovic et al.[65] (1989) Cefadroxil 25 mg/kg PO BID (maximum 2 g/day) vs phenoxymethyl-penicillin 25,000 U/kg PO TID	MC, RCT Pediatric patients aged 3 months to 18 years with acute tonsillo-pharyngitis caused by group A streptococci	N=150 10 days	Primary: Microbiological failure rate, persistent clinical symptoms	Primary: Microbiological failure rate was reported as 19.0% and 6.8% in patients treated with penicillin and cefadroxil, respectively (P<0.01). Of the patients with microbiological failure, persistent clinical symptoms of infection were reported as 43.5% and 25.0% in these patients treated with penicillin and cefadroxil, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(maximum 1.2 million U/day)				
Block et al.[63] (2000) Cefdinir 14 mg/kg/day PO divided BID (for 5 days) vs cefprozil 30 mg/kg/day PO divided BID (for 10 days)	DB, MC, PRO Pediatric patients aged 6 months to 12 years with acute otitis media	N=373 5 to 10 days	Primary: Clinical cure Secondary: Adverse events	Primary: At the end of therapy (study days 9 to 11), clinical efficacy was reported as 80.0% and 82.5% in patients treated with cefdinir and cefprozil (P= NS). Secondary: Diarrhea and overall adverse events were reported in cefdinir-treated patients (7.8% and 13%, respectively) and cefprozil-treated patients (4.2% and 12%, respectively; P=0.116).
Gwaltney et al.[66] (1997) Cefdinir 600 mg PO QD vs cefdinir 300 mg PO BID vs amoxicillin-clavulanate 500 mg PO TID In study A and B, participants received either one of the cefdinir	2 DB, MC, RCT Patients ≥13 years of age with acute community-acquired bacterial sinusitis with a duration of equal to or less than 4 weeks	N=1,446 10 days	Primary: Clinical response, microbiologic eradication rates Secondary: Adverse events	Primary: At the 7- to 14-day posttreatment evaluation and at the 3- to 5-week posttreatment evaluation, there was no statistically significant difference in clinical efficacy for the three treatment groups (approximately 90% response rate for all groups). At the 3- to 5-week post treatment evaluation, overall clinical response rates by pathogen were reported as 94%, 88%, and 92% for patients treated with cefdinir QD, cefdinir BID, and amoxicillin-clavulanate, respectively (P=0.007 and P=0.05 for cefdinir QD and amoxicillin-clavulanate vs cefdinir BID, respectively; P=0.35 for cefdinir QD vs amoxicillin-clavulanate). Microbiologic eradication rates were ≥90% for all treatment groups against pathogens other than *H influenzae*; eradication rates against *H influenzae* were reported at 78% and 57% for both cefdinir regimens and amoxicillin-clavulanate, respectively. Secondary: Adverse events requiring discontinuation of the study medication were reported as 1%, 3%, and 5% in patients treated with cefdinir QD, cefdinir BID, and amoxicillin-clavulanate, respectively (P=0.002 for the combined cefdinir groups vs amoxicillin-clavulanate groups).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
regimens or amoxicillin-clavulanate				
Brook[67] (2005) Cefdinir 600 mg (adults) or 14 mg/kg (pediatrics) PO QD (for 10 days) vs cefdinir 300 mg (adults) or 7 mg/kg (pediatrics) PO BID (for 5 to 10 days) vs penicillin 250 mg (adults) or 10 mg/kg (pediatrics) PO QID (for 10 days) In studies A through D, participants received either cefdinir or penicillin.	4 SB/DB, MC, PC, RCT Patients with throat pain, erythema, and a positive rapid streptococcal screening test Study A and B participants were <13 years of age. Study C and D participants were ≥13 years of age.	N=2,751 5 to 10 days	Primary: Clinical cure rate, bacterial eradication rate Secondary: Adverse events	Primary: Combined clinical cure rate was reported as higher for patients treated with cefdinir compared to patients treated with penicillin (94% vs 83%, respectively; P<0.001). Combined bacterial eradication rate was higher for patients treated with cefdinir compared to patients treated with penicillin (92% vs 77%, respectively; P<0.001). Secondary: All treatments were well tolerated; 98% of patients completed the treatment regimens. Patients treated with cefdinir reported diarrhea, nausea, headache, and vaginal moniliasis; patients treated with penicillin reported diarrhea, nausea, headache, and vomiting.
Asmar et al.[64] (1994)	DB, MC, PRO, RCT	N=368 10 days	Primary: Clinical evaluations,	Primary: On days 12 through 15, clinical cure or improvement was reported in 83% and 81% of patients treated with cefpodoxime and cefixime, respectively

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cefixime oral suspension 8 mg/kg/day PO QD vs cefpodoxime oral suspension 10 mg/kg/day PO QD	Patients aged 2 months to 17 years with acute suppurative otitis media		microbiologic evaluations Secondary: Adverse events	(P=0.541). On days 12 to 15, end-of-therapy response rates were reported as 53% and 51% in patients treated with cefpodoxime and cefixime, respectively (P=0.404). Overall microbiologic susceptibility was reported as 89% and 86% in patients treated with cefpodoxime and cefixime, respectively (P=0.70). Secondary: Drug-related adverse effects (e.g., diarrhea, diaper rash, vomiting and rash) occurred in 23.3% and 17.9% of patients taking cefpodoxime and cefixime, respectively.
Mendelman et al.[68] (1992) Cefpodoxime 10 mg/kg/day PO BID (maximum: 400 mg/day) vs amoxicillin 40 mg/kg and clavulanate 10mg/kg (combination entity) PO every 8 hours (maximum amoxicillin dose: 1,500 mg/day)	DB, MC, RCT Patients aged 2 months to 18 years with acute suppurative otitis media	N=146 10 to 14 days	Primary: Clinical response rates, microbiologic eradication rates Secondary: Adverse events	Primary: At days 10 to 14, clinical response rates for patients treated with cefpodoxime and amoxicillin-clavulanate, respectively, (P=0.57) were reported as follows: cured (68% vs 65%), improved (24% vs 23%), and failed (8% vs 13%). Recurrence rates for patients treated with cefpodoxime and amoxicillin-clavulanate were 24% and 25%, respectively. At days 10 to 14, microbiologic eradication rates were reported as 92% and 86% in patients treated with cefpodoxime and amoxicillin-clavulanate, respectively (P=0.14). Secondary: Drug-related adverse events were reported in 20.9% and 31.6% of patients treated with cefpodoxime and amoxicillin-clavulanate, respectively (P=0.102).
Pichichero et al.[69] (1994) Cefpodoxime suspension 10	DB, MC, PRO, RCT' Patients aged 2 to 17 years with acute	N=484 5 to 10 days	Primary: Clinical efficacy, bacteriologic efficacy	Primary: Clinical efficacy was reported as 96%, 94%, and 91% for patients treated with cefpodoxime (10 days), cefpodoxime (5 days), and penicillin, respectively (P=NS). At study days 5 to 10, bacteriologic eradication rates were reported as 95%, 90%, and 78% for patients treated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/day PO divided in 2 doses (for 5 days; maximum of 200 mg/day) vs cefpodoxime suspension 10 mg/kg/day PO as 1 dose (for 10 days; maximum of 200 mg/day) vs penicillin suspension 40 mg/kg/day PO divided into 3 doses (for 10 days; maximum 1 g/day)	tonsillo-pharyngitis		Secondary: Adverse events	cefpodoxime (10 days), cefpodoxime (5 days), and penicillin, respectively [*P*=0.003 and P=0.02 for cefpodoxime (10 days) and cefpodoxime (5 days) vs penicillin, respectively]. By the 32- to 38-day post treatment visit, cumulative bacteriologic failure rate was reported as 17%, 19%, and 35% for patients treated with cefpodoxime (10 days), cefpodoxime (5 days), and penicillin, respectively (P=0.001 and P=0.005 for cefpodoxime (10 days) and cefpodoxime (5 days) vs penicillin, respectively). Secondary: All treatments were well-tolerated. Gastrointestinal symptoms were most commonly reported.
Adelglass et al.[70] (1998) Cefprozil 500 mg PO BID vs amoxicillin-clavulanate 500 mg/125 mg PO TID	MC, OL, RCT Patients ≥13 years of age with severe acute bacterial sinusitis	N=219 10 days	Primary: Satisfactory clinical response Secondary: Adverse events	Primary; At day 10, satisfactory clinical response was reported in 84.5% and 89.9% of patients taking cefprozil and amoxicillin-clavulanate, respectively (P=NS). Two weeks post treatment, satisfactory clinical responses were reported as 80.8% and 81% of patients taking cefprozil and amoxicillin-clavulanate, respectively (P=NS). Relapse was reported in 3.1% and 8.6% of patients treated with cefprozil and amoxicillin-clavulanate, respectively (P=NS). Secondary: More patients treated with amoxicillin-clavulanate reported adverse events compared to patients treated with cefprozil (P<0.001); adverse events included diarrhea (P<0.001), nausea (P<0.042), and rash (P<0.035).
Pichichero et al.[71]	DB, MC, PRO,	N=426	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1995) Ceftibuten suspension 9 mg/kg PO QD vs penicillin V 25/mg/kg/day PO in 3 divided doses	RCT Pediatric patients aged 3 to 18 with symptomatic pharyngitis and scarlet fever caused by group A β-hemolytic streptococci	10 days	Clinical efficacy, microbiologic eradication Secondary: Adverse events	At 5 to 7 days post treatment, clinical efficacy was reported as 97% and 89% in patients treated with ceftibuten and penicillin, respectively (P<0.01); microbiologic eradication was reported as 91% and 80%, respectively (P<0.01). Secondary: Drug-related adverse events were similar between treatment groups; vomiting was the most commonly reported adverse event.
Varsano et al.[72] (1997) Ceftriaxone 50 mg/kg IM for 1 dose; then after 48 hours, if necessary, ceftriaxone 50 mg/kg for a second dose vs amoxicillin-clavulanate 12.5 mg PO TID (for 10 days)	MC, PRO, RCT Pediatric patients aged 4 months to 6 years with acute otitis media	N=215 1 to 10 days	Primary: Clinical failure rate, recurrence rate Secondary: Adverse effects, compliance, therapy preference	Primary: Clinical failure rate was reported as 4.6% and 4.7% for patients treated with ceftriaxone and amoxicillin-clavulanate, respectively (P=NS). Recurrence rate of acute otitis media between days 31 and 90 was reported as 29.4% and 13.6% in patients treated with amoxicillin-clavulanate and ceftriaxone, respectively (P=0.012). Secondary: Gastrointestinal side effects of diarrhea (17 vs 3 patients, respectively; P=0.002) and vomiting (12 vs 1 patient(s), respectively; P=0.004) were reported in more patients treated with amoxicillin-clavulanate compared to ceftriaxone. On study day 11, 79 of 106 patients either took amoxicillin-clavulanate as prescribed or in excess; the remaining patients used 82% to 95% of the prescribed volume. More parents, particularly parents of children treated in the ceftriaxone study group, preferred the intramuscular therapy over the oral therapy (68% vs 32%, respectively; P=0.0001).
Camacho et al.[73] (1992) Cefuroxime 250 mg PO BID	DB, MC, PG, RCT Patients ≥18 years of age with acute bacterial maxillary sinusitis with a	N=239 10 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary:	Primary: Clinical efficacy was reported as 85% and 82% in patients treated with cefuroxime or amoxicillin-clavulanate, respectively (P=0.446). Bacteriologic efficacy was reported as 84% and 87% of patients treated with cefuroxime and amoxicillin-clavulanate, respectively (P=0.567).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amoxicillin-clavulanate 500 mg PO TID	duration of less than 30 days		Adverse events	Secondary: Drug-related adverse events were reported as 3% and 13% for patients treated with cefuroxime and amoxicillin-clavulanate, respectively (P=0.001), particularly for diarrhea (1% vs 3%, respectively; P=0.001).
Aujard et al.[74] (1995) Cefuroxime suspension 20 mg/kg/day PO divided BID (maximum 500 mg/day; for 4 days) vs penicillin suspension 45 mg/kg/day PO divided TID (for 10 days)	MC, PRO, RCT Pediatric patients aged 2 to 15 years with group A β-hemolytic streptococcal pharyngitis	N=200 4 to 10 days	Primary: Clinical cure, microbiological cure Secondary: Adverse events	Primary: At 2 to 4 days post-treatment, clinical cure rates were reported as 94.8% and 96.1% of patients treated with cefuroxime and penicillin, respectively (P=NS). At 2 to 4 days post-treatment, microbiological eradication was reported as 87.6% and 87.4% in patients treated with cefuroxime and penicillin, respectively (P=NS); at 28 to 33 days post-treatment, microbiological eradication was reported as 94.4% and 91.9%, respectively (P=NS). Clinical success in terms of resolution of sore throat and dysphagia occurred more rapidly in patients treated with cefuroxime compared to penicillin (P=0.024 and P=0.027, respectively). Secondary: Both treatments were well tolerated. Drug-related adverse events were reported in 2.1% and 2.7% of patients treated with cefuroxime and penicillin, respectively (P=NS).
Disney et al.[75] (1992) Cephalexin 27 mg/kg/day PO divided in 4 doses vs penicillin 27 mg/kg/day PO divided in 4 doses	DB, MC, RETRO, RCT, XO Patients aged 4 to 17 years with group A β-hemolytic streptococcal tonsillopharyngitis	N=525 10 days	Primary: Symptomatic clinical failure, bacteriologic failure rate, combined failure rate	Primary: Symptomatic clinical failure rate was reported as 8% and 3% in patients treated with penicillin and cephalexin, respectively (P=0.01); bacteriologic failure rate was reported as 11% and 7%, respectively (P=0.10). Combined failure rate was 19% and 10% in patients treated with penicillin and cephalexin, respectively (P=0.004).
Respiratory Infections—Lower Respiratory Tract				
ZeLuff et al.[77]	PRO, RCT	N=103	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1986) Cefaclor 500 mg PO every 8 hours vs cefadroxil 1 g PO every 12 hours	Black African gold miners aged 13 to 59 years with pneumococcal pneumonia confirmed by culture/serology	10 days	Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Clinical cure was reported as 94% of patients treated with either cefadroxil or cefaclor. Microbiologic cure was reported in 98% and 96% of patients treated with cefadroxil and cefaclor, respectively. Secondary: One patient treated with cefaclor withdrew from the study due to severe diarrhea. Otherwise, minimal side effects were reported for both therapies.
Drehobl et al.[78] (1997) Cefaclor 500 mg PO TID vs cefdinir 300 mg PO BID	DB, MC, RCT Patients with community acquired-pneumonia	N=538 10 days	Primary: Clinical response, microbiological eradication Secondary: Adverse events	Primary: Satisfactory clinical response was reported as 89% and 86% of patients treated with cefdinir and cefaclor, respectively; microbiological eradication was reported as 92% and 93%, respectively. For all comparisons, P=NS. Secondary: Patients taking cefdinir reported a higher incidence of diarrhea compared to patients treated with cefaclor (13.7% vs 5.3%, respectively; P<0.001).
Phillips et al.[79] (1993) Cefaclor 250 mg PO TID vs cefpodoxime 200 mg PO BID	DB, MC, RCT Patients with signs and symptoms of acute bacterial exacerbation of COPD	N=301 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: There were no statistically significant differences between cefpodoxime and cefaclor in the eradication of the original pathogen (91% vs 92%, respectively) or in clinical response at 3 to 7 days post-treatment (99% vs 92%, respectively). More bacterial isolates were susceptible to cefpodoxime compared to cefaclor (91% vs 84%, respectively; P<0.001). Secondary: There were no significant differences between cefpodoxime and cefaclor in adverse events (11% vs 12%, respectively).
Chirurgi et al.[80] (1991) Cefaclor 250 mg PO every 8 hours	PRO, RCT Patients with acute bronchitis, not pneumonia	N=45 7 to 14 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary:	Primary: Clinical efficacy was reported as 87.5% and 92.3% of patients treated with ceftibuten and cefaclor, respectively. Bacteriologic efficacy was reported as 87.5% and 80.0% of patients treated with ceftibuten and cefaclor, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ceftibuten 400 mg PO QD			Adverse events	Secondary: The rates of adverse events were reported as 7.9% and 5.6% in patients treated with ceftibuten and cefaclor, respectively.
Ball[94] (1994) Cefaclor 500 mg PO every 8 hours vs cefprozil 500 mg PO every 12 hours vs cefuroxime 500 mg PO every 12 hours vs amoxicillin-clavulanate PO 500 mg every 8 hours In study A, participants received either cefprozil or cefaclor. In study B, participants received either cefprozil or cefuroxime. Study	3 MC, PRO Patients ≥18 years of age with acute mild-to-moderate respiratory tract infections, including acute bronchitis, acute exacerbations of chronic bronchitis, and bacterial pneumonia	N=1,352 5 to 10 days	Primary: Clinical efficacy, bacteriological efficacy Secondary: Adverse effects	Primary: In study A, clinical efficacy in acute bronchitis was reported as 88% for patients treated with either cefprozil or cefaclor; bacteriological eradication was reported as 86% and 82%, respectively. Clinical efficacy in acute exacerbation of chronic bronchitis was reported as 80% and 62% in patients treated with cefprozil and cefaclor, respectively (P=0.067); bacteriological eradication was reported as 62% and 74%, respectively. Clinical efficacy in pneumonia was reported as 82% and 79% in patients treated with cefprozil and cefaclor, respectively; bacteriological eradication was reported as 82% and 71%, respectively. In study B, clinical efficacy was reported as 95% and 84% for patients treated every 12 hours with cefprozil and cefuroxime, respectively (P<0.03); bacteriologic eradication was reported as 100% and 75%, respectively. In study C, clinical and bacteriological efficacy was similar between cefprozil and amoxicillin-clavulanate both given every 8 hours; P=NS. Secondary: All treatment regimens were well-tolerated. In study C, diarrhea was reported more frequently in patients treated with amoxicillin-clavulanate compared to patients treated with cefprozil (19% vs 7%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
C participants received either cefprozil or amoxicillin-clavulanate.				
Blaser et el.[81] (1983) Cefadroxil 500 mg PO BID vs cephalexin 250 mg PO QID	PRO, RCT Patients aged 19 to 92 years with community-acquired pneumonia of mild to moderate severity	N=34 10 days	Primary: Clinical evaluation, microbiologic evaluation Secondary: Adverse events	Primary: All 34 cases achieved clinical cure; no additional information in regards to differences in clinical cure rates were reported between cefadroxil and cephalexin. Clearing of chest exam findings were reported in 79% and 73% of patients treated with cefadroxil and cephalexin, respectively. Secondary: Drug-related adverse effects were minimal.
Fogarty et al.[82] (2000) Cefdinir 300 mg PO BID (for 5 days) vs cefprozil 500 mg PO BID (for 10 days)	DB, MC, PRO, RCT Patients with acute exacerbations of chronic bronchitis	N=281 5 to 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: The observed clinical cure rate among cefdinir-treated patients was 80% compared to 72% of cefprozil-treated patients (95% CI, -1.6% to 18.3%). The overall rates of microbiological eradication of pathogens were 81% for cefdinir-treated patients and 84% for cefprozil-treated patients (95% CI: –10.0% to 5%). Secondary: Safety of the drugs was analyzed for all patients who received study medication. Of these patients, 95 (34%) patients receiving cefdinir and 89 (33%) patients receiving cefprozil experienced at least one adverse event during treatment (P=0.90). The most frequent adverse events on therapy for both cefdinir- and cefprozil-treated patients were diarrhea and headache. Seventeen percent of cefdinir-treated patients and 6% of cefprozil-treated patients experienced diarrhea during treatment (P<0.01).
Alvarez-Sala et al.[83] (2006)	DB, DD, PG, RCT Patients ≥18 years of age with acute	N=541 5 to 10 days	Primary: Clinical evaluation, bacteriologic	Primary: On day 11, clinical success rate was reported as 79.9% and 82.7% for patients treated with cefditoren and cefuroxime, respectively (P=NS). On day 30, clinical success rate was reported as 81% and 85.5% for patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cefditoren 200 mg PO BID (for 5 days) vs cefuroxime 250 mg PO BID (for 10 days)	exacerbations of chronic bronchitis		evaluation Secondary: Adverse events	treated with cefditoren and cefuroxime, respectively (P=NS). On day 11, bacteriological response was reported as 72.8% and 67.0% for patients treated with cefditoren and cefuroxime, respectively (P=NS). Secondary: Drug-related adverse events were reported in 7.7% and 11.4% of patients treated with cefditoren and cefuroxime, respectively.
Fogarty et al.[89] (2002) Cefditoren 200 mg PO BID vs cefditoren 400 mg PO BID vs amoxicillin-clavulanate 875/125 mg PO BID	DB, MC, PG, PRO, RCT Adult outpatients with community-acquired pneumonia	N=445 14 days	Primary: Clinical cure rates, microbiologic eradication rate Secondary: Adverse events	Primary: Within 48 hours of treatment completion, clinical cure was reported as 88.0%, 89.9%, and 90.3% for patients treated with cefditoren (200 mg), cefditoren (400 mg), and amoxicillin-clavulanate, respectively; at 7 to 14 days post-treatment, clinical cure was reported as 86.5%, 86.8%, and 87.8%, respectively. At 7 to 14 days post treatment, microbiologic eradication was reported as 84.0%, 88.6%, and 82.6% was patients treated with cefditoren (200 mg), cefditoren (400 mg), and amoxicillin-clavulanate, respectively. For all comparisons, P=NS. Secondary: All treatments were well tolerated. Due to an adverse event, 4.9%, 3.0%, and 5.2% of patients treated with cefditoren (200 mg), cefditoren (400 mg), and amoxicillin-clavulanate, respectively, discontinued therapy.
Leophonte et al.[84] (1993) Cefepime 1 g IV/IM BID vs ceftazidime 1 g IV/IM TID	AC, MC, OL, RCT Adult patients with moderate to severe community-acquired lower respiratory tract infections	N=111 1 to 15 days	Primary: Clinical cure rate, pathogen eradication rate Secondary: Adverse events	Primary: Clinical cure was reported in 87% and 86% of patients treated with cefepime and ceftazidime, respectively (P=0.8); pathogen eradication rates were reported as 95% for both treatment groups (P=0.7). Secondary: Both treatments were well tolerated and a similar incidence of adverse events.
Grossman et al.[85]	DB, MC, PRO,	N=151	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1999) Cefepime 2 g every 12 hours vs ceftriaxone 1 g every 12 hours	RCT Patients ≥65 years of age who had been admitted to the hospital after being diagnosed with community-acquired pneumonia	3 to 14 days	Clinical response, bacteriologic eradication Secondary: Adverse events	Clinical response was reported as 79.1% and 75.4% in patients treated with cefepime and ceftriaxone, respectively (P=0.62). Relative to evaluable study participants, all but 1 patient treated with cefepime achieved bacteriologic eradication. Secondary: There was no statistically significant difference in the incidence of adverse events reported by patients treated with either cefepime or ceftriaxone (76.3% vs 84%, respectively; P=0.24). Diarrhea was the most common adverse event reported in patients treated with cefepime and ceftriaxone (5 vs 2 patients, respectively).
Bradley et al.[95] (2001) Cefepime 50 mg/kg IV every 8 hours (maximum 6 g/day) vs cefepime 50 mg/kg IV every 12 hours (maximum 4 g/day) vs cefotaxime 120 mg/kg/day IV in 4 divided doses (maximum 4.5 g/day) vs ceftazidime 150	4 trials MC/OL/ RCT Pediatric patients aged 2 months to 18 years old with serous lower respiratory tract infections	N=646 Up to 21 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: In study A, clinical efficacy was reported as 91% for patients treated with cefepime; bacteriologic eradication was 93%. In study B, clinical efficacy, at the end of treatment, was reported as 100% for patients treated with cefepime and cefuroxime; bacteriologic eradication was also reported as 100%. The study consisted of 10 evaluable study participants. In study C, clinical efficacy was 100% for patients treated with either cefepime or cefotaxime; bacteriologic eradication was reported in 75% and 100% of patients treated with cefepime and cefotaxime, respectively. The study consisted of 13 evaluable study participants. In study D, clinical efficacy was reported, at the end of treatment, as 93% and 95% of patients treated with cefepime and ceftazidime, respectively; bacteriologic eradication was reported as 95% and 100%, respectively. Secondary: Overall, adverse events reported by study participants were generally mild except for 1 case of rash and 1 case of vaginitis for patients treated with cefepime.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/day IV in 3 divided doses (maximum 6 g/day) vs cefuroxime 100 mg/kg/day IV in 3 divided doses (maximum 4.5 g/day) vs placebo In study A, participants received either cefepime every 8 or 12 hours. In studies B, C, and D, participants received either cefepime or a comparator (cefuroxime, cefotaxime, ceftazidime, respectively).				
Paladino et al.[126] (2007) Cefepime 1 g IM every 24 hours	RCT, DB Patients aged 60 and older with nursing home-acquired	N=69 10-14 days	Primary: Clinical success (cure or improvement) and safety	Primary: Clinical success occurred in 78% of cefepime- and 66% of ceftriaxone-treated patients (P=0.39). Ninety-three percent of patients were switched to oral antibiotics after 3

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ceftriaxone 1 g IM every 24 hours After 3 days, patients with objective evidence of improvement could be switched to oral antibiotics.	pneumonia who did not require hospitalization			days. Most patients experienced mild to no discomfort at the site of IM injection of ceftriaxone or cefepime; if present, it abated quickly. One patient with a history of diabetes mellitus had high blood glucose while receiving ceftriaxone. Other drug-related adverse events occurred rarely and only with the oral antibiotics. The overall mortality rate was 8%.
Verghese et al.[86] (1990) Cefixime 400 mg PO for 1 dose vs cephalexin 250 mg PO QID	RCT Patients with purulent exacerbation of chronic bronchitis	N=86 1 to 14 days	Primary: Clinical cure, clinical improvement Secondary: Adverse events	Primary: Clinical cure was reported as 70.8% and 50.0% in patients treated with cefixime and cephalexin, respectively (P<0.05). Combined percentages for clinical cure and improvement were reported as 95.8% and 84.2% in patients treated with cefixime and cephalexin, respectively (P=0.06). Secondary: Both treatments were well tolerated. Diarrhea occurred more often in patients treated with cefixime compared to patients treated with cephalexin (P=0.013).
Sengupta et al.[87] (2004) Cefixime 4 mg/kg PO BID vs cefpodoxime 5 mg/kg PO BID	AC, MC, OL, PRO, RCT Pediatric patients aged 6 months to 12 years with community-acquired lower respiratory tract infections, including community-acquired pneumonia and acute exacer-bations of chronic bronchitis	N=776 10 to 14 days	Primary: Clinical cure, bacteriologic eradication Secondary: Adverse events	Primary: Clinical cure was reported as 97.0% and 86.8% for patients treated with cefpodoxime and cefixime, respectively; bacteriologic eradication was reported as 93.4% and 82.9%, respectively. Secondary: Both treatments were well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Zuck et al.[88] (1999) Cefixime 200 mg PO BID vs cefuroxime 250 mg PO BID	DB, MC, PG, RCT Hospitalized patients 30 to 75 years of age experiencing acute exacerbations of chronic bronchitis	N=58 8 days	Primary: Clinical cure, microbiological eradication Secondary: Adverse events	Primary: At 2 to 4 days post-treatment, clinical cure was reported in 94% and 71% of patients treated with cefuroxime and cefixime, respectively (P=NS); microbiological eradication occurred more quickly in patients treated with cefuroxime compared to cefixime (P=0.002 at 2 to 4 weeks post-treatment). Secondary: Both treatments were well tolerated. One patient treated with cefuroxime reported fever; one patient treated with cefixime reported buccal mycosis.
File et al.[135] (2011) Ceftaroline 600 mg IV every 12 hours for 5 to 7 days vs ceftriaxone 1 g IV every 24 hours for 5 to 7 days Patients also received two 500 mg doses of oral clarithromycin every 12 hours on day 1.	RCT, DB, MC, AC Patients hospitalized in a non-intensive care unit setting with community-acquired pneumonia (CAP) of PORT risk class III or IV	N=613 Variable duration	Primary: Clinical cure rates at the test-of-cure (TOC) visit (8–15 days post-therapy) in the clinically evaluable (CE) and modified intent-to-treat efficacy (MITTE) populations Secondary: Clinical cure in the microbiologically evaluable (ME) and microbiological modified intent-to-treat efficacy (mMITTE) populations, overall success rate, clinical and microbiological response by pathogen, clinical	Primary: Clinical cure rates were 86.6% for ceftaroline and 78.2% for ceftriaxone in the CE population (95% CI, 1.4 to 15.4). Clinical cure rates in the MITTE population were 83.8% for ceftaroline and 77.7% for ceftriaxone (95% CI, -0.2 to 12.6). Secondary: Clinical cure was observed in 89.9% and 76.1% of patients in the ceftaroline and ceftriaxone groups, respectively, in the ME population (95% CI, 1.3 to 26.4). In the mMITTE population, clinical cure was observed in 88.0% and 75.0% of patients in the ceftaroline and ceftriaxone groups, respectively (95% CI, 0.7 to 25.2). At the TOC visit, overall (clinical and radiographic) success was observed in 86.6% of patients in the ceftaroline group and 78.2% of patients in the ceftriaxone group in the CE population (95% CI, 1.4 to 15.4). In the MITTE population, 83.5% of ceftaroline patients and 77.7% of ceftriaxone patients experienced overall success (95% CI, -0.6 to 12.2). At the LFU visit, clinical relapse was noted in 1.1% of patients in the ceftaroline group and 1.8% of patients in the ceftriaxone group (95% CI, -4.2 to 2.4) of the CE population. In the MITTE population, 1.2% of patients in the ceftaroline group and 1.3% of patients in the ceftriaxone group (95% CI, -2.6 to 2.4) were considered a clinical relapse. Per-patient favorable microbiological response rates in the ME population were 89.9% in the ceftaroline group compared with 78.9% in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			relapse at the late follow-up (LFU) visit, and safety	ceftriaxone group (95% CI, -1.2 to 23.3). Consistent results were observed in the mMITTE population; 88.0% in the ceftaroline group and 78.8% in the ceftriaxone group (95% CI, -2.7 to 21.1). The most common AEs for ceftaroline-treated patients were diarrhea, headache, insomnia and nausea, compared with hypokalemia, hypertension, nausea and diarrhea for ceftriaxone-treated patients. The most common study drug-related treatment-emergent AEs were diarrhea (4.4% for ceftaroline and 1.0% for ceftriaxone), sinus bradycardia (1.0% for ceftaroline and 1.0% for ceftriaxone), nausea (1.3% for ceftaroline and 0.6% for ceftriaxone) and phlebitis (1.3% for ceftaroline and 0.6% for ceftriaxone).
Low et al.[136] (2011) Ceftaroline 600 mg IV every 12 hours for up to 7 days vs ceftriaxone 1 g IV every 24 hours for up to 7 days	RCT, DB, MC, AC Patients hospitalized in a non-intensive care unit setting with community-acquired pneumonia (CAP) of PORT risk class III or IV	N=627 Variable duration	Primary: Clinical cure rates at the test-of-cure (TOC) visit (8–15 days post-therapy) in the clinically evaluable (CE) and modified intent-to-treat efficacy (MITTE) populations Secondary: Clinical cure in the microbiologically evaluable (ME) and microbiological modified intent-to-treat efficacy (mMITTE) populations, overall success rate, clinical and microbiological	Primary: Clinical cure rates were 82.1% for ceftaroline and 77.2% for ceftriaxone in the CE population (95% CI, -2.5 to 12.5). Clinical cure rates in the MITTE population were 81.3% for ceftaroline and 75.5% for ceftriaxone (95% CI, -1.0 to 12.7). Secondary: Clinical cure was observed in 81.2% and 75.0% of patients in the ceftaroline and ceftriaxone groups, respectively, in the ME population (95% CI, -6.7 to 19.2). In the mMITTE population, clinical cure was observed in 80.0% and 75.0% of patients in the ceftaroline and ceftriaxone groups, respectively (95% CI, -7.4 to 17.4). Clinical cure rates at the EOT were 86.0% for ceftaroline and 80.0% for ceftriaxone in the CE population (95% CI, -1.0 to 13.0). Clinical cure rates were 86.2% for ceftaroline and 78.8% for ceftriaxone in the MITTE population at the EOT (95% CI, 1.1 to 13.8). At the TOC visit, the overall (clinical and radiographic) success rates were 81.7% for ceftaroline and 77.2% ceftriaxone in the CE population (95% CI, -3.0 to 12.1). Overall success rates were 81.0% with ceftaroline and 75.5% with ceftriaxone in the MITTE population (95% CI, -1.3 to 12.4). Clinical relapse at the LFU visit was reported for 2.8% of patients in the ceftaroline group and 0.6% of patients in the ceftriaxone group of the CE

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			response by pathogen, clinical relapse at the late follow-up (LFU) visit, and safety	population (95% CI, -1.0 to 5.8). In the MITTE population, clinical relapse was determined in 2.1% of patients in the ceftaroline group and 1.0% of patients in the ceftriaxone group (95% CI, -1.6 to 4.0). Favorable per-patient microbiological response rates were observed for 84.7% of patients in the ceftaroline group and 82.9% of patients in the ceftriaxone group in the ME population (95% CI, -9.7 to 13.7). In the mMITTE population, 82.2% of patients in the ceftaroline group and 81.8% of patients in the ceftriaxone group had a favorable microbiological response rate (95% CI, -11.1 to 11.9). There were no occurrences of microbiological reinfection or recurrence at the LFU visit. The most common AEs for ceftaroline-treated patients were diarrhea, headache, hypokalemia, insomnia and phlebitis, compared with diarrhea, hypertension, insomnia and phlebitis for ceftriaxone-treated patients. Similar incidence rates of SAEs were demonstrated across both treatment groups (13.0% for ceftaroline vs 12.7% for ceftriaxone).
File et al.[138] (2010) Ceftaroline 600 mg IV every 12 hours for up to 7 days vs ceftriaxone 1 g IV every 24 hours for up to 7 days Patients in FOCUS 1 received two 500 mg doses of oral clarithromycin every 12 hours on	Pooled analysis (2 trials) Patients hospitalized in a non-intensive care unit setting with community-acquired pneumonia (CAP) of PORT risk class III or IV	N=1,228 Variable duration	Primary: Clinical cure rates at the test-of-cure (TOC) visit (8–15 days post-therapy) in the clinically evaluable (CE) and modified intent-to-treat efficacy (MITTE) populations Secondary: Clinical cure in the microbiologically evaluable (ME) and microbiological	Primary: Clinical cure rates were 6.7% (95% CI, 1.6 to 11.8) and 6.0% (95% CI, 1.4 to 10.7) higher for ceftaroline than for ceftriaxone in the CE and MITTE populations, respectively. Secondary: Clinical cure rates in the ME and mMITTE populations were 85.1% and 83.6%, respectively, for ceftaroline, compared with 75.5% and 75.0%, respectively, for ceftriaxone. Clinical relapse rates at LFU were 1.9% for ceftaroline and 1.2% for ceftriaxone in the CE population (95% CI, -1.4 to 2.9). Clinical relapse rates were 1.7% for ceftaroline and 1.1% for ceftriaxone in the MITTE population (95% CI, -1.2 to 2.3). Favorable per-patient microbiological response rates in the ME population were 87.0% for ceftaroline and 81.0% for ceftriaxone (95% CI, -2.3 to 14.6). In the MITTE population, microbiological response rates were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
day 1.			modified intent-to-treat efficacy (mMITTE) populations, clinical and microbiological clinical relapse at the late follow-up (LFU) visit, and safety	84.8% for ceftaroline and 80.4% for ceftriaxone (95% CI, -3.7 to 12.8). The incidences of treatment-emergent AEs were similar among the treatment groups. The most common AEs were diarrhea, headache, and insomnia for patients receiving ceftaroline and diarrhea, hypertension, and hypokalemia for patients receiving ceftriaxone.
McAdoo et al.[90] (1998) Ceftibuten 400 mg PO QD vs amoxicillin-clavulanate 500 mg PO TID	DB, MC, RCT Patients ≥18 years of age with acute exacerbations of chronic bronchitis	N=369 5 to 15 days	Primary: Clinical response, microbiologic response Secondary: Adverse events	Primary: At 7 to 21 days post-treatment, clinical success rates were reported as 84% and 79% in patients treated with ceftibuten and amoxicillin-clavulanate, respectively (P=NS). At 7 to 21 days post-treatment, microbiologic response rates were reported as 97% and 86% in patients treated with ceftibuten and amoxicillin-clavulanate, respectively (P=NS). Secondary: Drug-related adverse events most commonly reported for patients treated with ceftibuten and amoxicillin-clavulanate were gastrointestinal (15% vs 24%, respectively).
Ziering et al.[91] (1998) Ceftibuten 400 mg PO QD vs clarithromycin 500 mg PO BID	DB, MC, PG Patients ≥18 years of age with acute exacerbations of chronic bronchitis	N=309 7 to 14 days	Primary: Clinical assessment, microbiological assessment, overall success rate Secondary: Adverse events	Primary: At the end of the treatment, clinical success was reported in 91% and 93% of patients treated with ceftibuten and clarithromycin, respectively. At 7 to 21 days post-treatment, clinical cure was reported as 92.6% and 93.3%, respectively. Overall success rate was reported as 84.3% and 86.7%, respectively (P=NS). At the end of the treatment, microbiological eradication rates were reported in 84.8% and 89.5%, respectively. At 7 to 21 days post-treatment, microbiological eradication was reported as 100% in both treatment groups (P=NS). Secondary: Less patients treated with ceftibuten compared to clarithromycin reported drug-related adverse events (5.3% vs 21.9%, respectively; P<0.001) likely due to taste perversion associated with clarithromycin intake (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Brambilla et al.[92] (1992) Cefuroxime 750 mg IV TID (for 2 to 3 days), then cefuroxime 500 mg PO BID (for 5 days) vs amoxicillin-clavulanate 1.2 g IV TID (for 2 to 3 days), then 625 mg PO TID (for 5 days)	MC, PRO Hospitalized patients with pneumonia or acute exacerbations of chronic bronchitis or bronchiectasis	N=512 7 to 8 days	Primary: Clinical efficacy, bacteriological efficacy Secondary: Adverse events	Primary: Clinical efficacy was reported as 87.1% and 85.9% of patients treated with cefuroxime and amoxicillin-clavulanate, respectively. Bacteriological efficacy was reported as 72.8% and 70.0% in patients treated with cefuroxime and amoxicillin-clavulanate, respectively. Secondary: Both treatment regimens were well tolerated. Drug-related adverse events were reported in 5.0% and 4.3% of patients treated with cefuroxime and amoxicillin-clavulanate, respectively.
Henry et al.[93] (1995) Cefuroxime 250 mg PO BID (for 5 days) and placebo PO BID (for 5 days) vs cefuroxime 250 mg PO BID (for 10 days) vs amoxicillin-clavulanate 500	DB, MC, RCT Patients with secondary bacterial infections of acute bronchitis	N=423 5 to 10 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: Clinical success was reported as 82%, 86%, and 83% in patients treated with cefuroxime (5 days), cefuroxime (10 days), and amoxicillin-clavulanate, respectively. Microbiologic eradication was reported as 87%, 91%, and 86% in patients treated with cefuroxime (5 days), cefuroxime (10 days), and amoxicillin-clavulanate, respectively. Secondary: Patients treated with amoxicillin-clavulanate reported a higher incidence of drug-related adverse events compared to patients treated with cefuroxime (P=0.001). A greater incidence of diarrhea and nausea was reported for patients treated with amoxicillin-clavulanate compared to patients treated with cefuroxime (5 days) and cefuroxime (10 days); 37% vs 19%, vs 15%, respectively, P<0.001.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg PO TID (for 10 days)				
Miscellaneous Infections				
Nungu et al.[109] (1995) Cefadroxil 1 g/100 mL water PO 2 hours before surgery and 12 hours later vs cefuroxime 0.75 g IV 30 minutes prior to surgery and every 8 hours for 2 additional doses	PRO, RCT Patients undergoing intra- or subtrochanteric femoral hip fracture surgery	N=559 1 to 2 days	Primary: Absence or presence of surgical wound infection	Primary: One study participant treated with cefadroxil reported a case of superficial wound infection with methicillin-sensitive *S aureus*. Six study participants treated with cefuroxime reported infections post-surgery; the infections included both superficial and deep infections. The difference in efficacy for preventing infections between the two treatment groups was not statistically significant (P=0.07).
Jones et al.[116] (1987) Cefazolin 1 g IV bolus prior to surgery and cefazolin 1 g every 8 hours for 24 hours; cefazolin 1 g during surgery if surgery lasts longer than 2 hours vs cefotaxime 1 g IV bolus prior to	PRO, RCT, SB Patients ≥18 years of age undergoing elective surgery	N=914 2 days	Primary: Absence or presence of surgical wound infection Secondary: Adverse events	Primary: The mean time to onset of infection was reported as 9.9, 15.8, and 11.8 days for patients treated with cefazolin, cefoxitin, and cefotaxime, respectively. There was no statistically significant difference in wound infection morbidity rate for all treatment groups (P>0.05). Secondary: Although not statistically significant, a greater number of adverse events were reported in patients treated with cefoxitin vs cefazolin and cefazolin vs cefotaxime. Allergic reactions were most commonly reported with cefoxitin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
surgery; cefotaxime 1 g during surgery if surgery lasts longer than 2 hours vs cefoxitin 2 g IV bolus prior to surgery and cefoxitin 2 g every 6 hours for 24 hours				
Curtis et al.[110] (1993) Cefazolin 1 g IV 1 hour prior to surgery and every 8 hours (for 48 hours) plus cefazolin 1 g IV after 4 hours of surgery vs cefuroxime 1.5 g IV 1 hour prior to surgery plus cefuroxime 1.5 g every 12 hours for 3 additional doses	PRO, RCT Patients undergoing open heart surgery	N=702 2 to 3 days	Primary: Absence or presence of surgical wound infection (draining wound with or without positive culture)	Primary: There was no statistically significant difference in overall wound infection rate between treatment groups (P=0.68). Differences in infection rates for both treatment groups were reported as being not statistically significant for chest wound infections, true mediastinitis, and leg infections (P=0.79, P=0.84, P=0.83, respectively).
Jewesson et al.[111] (1996)	DB, PRO, RCT Patients ≥19 years	N=150 2 days	Primary: Absence or presence of	Primary: There was no clinical evidence of infection in 93% and 92% of patients treated with cefazolin and ceftizoxime, respectively (P=1.0). Clinical

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cefazolin 1 g in 100 mL 0.9% NaCl IV 30 minutes prior to surgery and cefazolin 1 g every 12 hours for 24 hours vs ceftizoxime 1 g in 100 mL 0.9% NaCl IV 30 minutes prior to surgery and ceftizoxime 1 g every 12 hours for 24 hours	of age undergoing elective biliary tract surgery		surgical wound infection	success of the treatments were not influenced by procedure type (P=0.48 to 0.59) nor the number of patients receiving less than 2 doses of the antibiotic (P=1.0).
Ozturk et al.[122] (2007) Cefazolin 1 g IV as a single dose vs cefuroxime 750 mg IV as a single dose vs ceftazidime 1 g IV as a single dose vs	RCT, PC Patients who underwent TURP for symptomatic benign prostatic hyperplasia	N=120 10 days	Primary: Clinical outcomes	Primary: The occurrence rates of fever were 10.3%, 16%, 13.7%, and 23.3% in the cefazolin, cefuroxime, ceftazidime and placebo groups, respectively (P>0.05). The urine culture on the 2nd postoperative day was positive only in 1 patient in the cefazolin group (3.4%) and in 2 patients in the placebo group. The 2nd-day, postoperative bacteriuria rates were similar in all groups. On the 10th postoperative day, a positive urine culture was observed in 10 patients in the cefazolin group (34%), 2 patients in the cefuroxime group (6.6%), 2 patients in the ceftazidime group (6.8%), and in 12 patients in the placebo group (40%) On the 10th day, the incidence rates of bacteriuria in the placebo group and the cefazolin group were similar (P=0.661). In the cefuroxime group, the bacteriuria incidence rate was 6.6%, and when compared with the placebo group, the difference was considered significant (P=0.002). The difference between the cefuroxime

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				and the ceftazidime groups was also significant (P=0.003). There were statistically significant differences between the cefazolin and cefuroxime group (P=0.008) as well as between the cefazolin and ceftazidime groups (P=0.01). All antibiotics were generally well tolerated in all patients, and there were no significant drug-related side effects.
Gentry et al.[117] (1991) Cefazolin 1 g IV every 8 hours (for 8 weeks) vs ceftazidime 2 g IV every 12 hours (for 4 weeks) vs ofloxacin 400 mg PO BID (for 4 weeks)	PG, RCT Patients with biopsy-confirmed nonprosthetic osteomyelitis caused by susceptible organisms	N=33 4 to 8 weeks	Primary: Infection relapse Secondary: Adverse events	Primary: Within 18 months of treatment completion, 74% and 86% of patients treated with oral ofloxacin and parenteral cephalosporin, respectively, achieved infection resolution without relapse. Secondary: Both treatments were well tolerated. Drug-related adverse events were reported in 37% and 29% of patients treated with oral ofloxacin and parenteral cephalosporins, respectively.
Huang et al.[112] (2002) Cefepime 2 g IV every 12 hours vs ceftazidime 2 g IV every 8 hours	OL, PRO, RCT Patients ≥18 years of age with severe infections including septicemia, urinary tract infection, bacterial bronchitis, bacterial pneumonia, intra-abdominal infection	N=42 10 to 14 days	Primary: Clinical response rates, bacteriological eradication rates Secondary: Adverse events	Primary: Clinical response rates of 71% and 61% were reported for patients treated with cefepime and ceftazidime, respectively. Bacteriological eradication rates were reported as 87.5% and 89.0% of patients treated with cefepime and ceftazidime, respectively. Clinical response and bacteriological eradication rates were not statistically different between treatment groups. Secondary: Adverse events reported with both treatments were minimal. The most common adverse events were hyperkalemia (12%), impaired liver biochemistry (12%), diarrhea (10%), and hypoalbuminemia (10%).

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Chandrasekar et al.[42] (2000) Cefepime 2 g IV every 8 hours vs ceftazidime 2 g IV every 8 hours	DB, MC, PRO, RCT Hospitalized patients ≥18 years of age with chemotherapy-induced neutropenia (absolute neutrophil count <500/mm^3) with fever	N=188 1 to 35 days	Primary: Presence or absence of febrile episodes, bacteremic clearance Secondary: Adverse events	Primary: Prevention of febrile episodes was reported in 57% and 60% of patients treated with cefepime and ceftazidime, respectively (P=0.77). Success rates in microbiologically documented infections were reported as 39% and 16% of patients treated with cefepime and ceftazidime, respectively (P=0.17). Bacteremic clearance was reported in 71% and 40% of patients treated with cefepime and ceftazidime, respectively (P=0.3). Treatment failure was reported in 43% and 40% of patients treated with cefepime and ceftazidime, respectively (P=NS). Of the treatment failures in microbiologically documented infections, 43% and 63% of patients treated with cefepime and ceftazidime, respectively, had resistant infections. Secondary: Overall non-drug-related mortality within 30 days of drug discontinuation of cefepime and ceftazidime was reported as 15% and 8%, respectively (P=0.06). The most common adverse effects of cefepime were rash, nausea and vomiting; for ceftazidime, rash and diarrhea.
Chuang et al.[43] (2002) Cefepime 50 mg/kg/dose IV BID to TID vs ceftazidime 50 mg/kg/dose IV BID to TID	OL, PRO, RCT Children aged 2 months to 15 years with chemotherapy-induced neutropenia (absolute neutrophil count <500/mm^3) with fever	N=96 3 to 20 days	Primary: Overall success rate of febrile prophylaxis, bacteremic clearances, new infection rate Secondary: Adverse events	Primary: After 72 hours of treatment, positive clinical response was reported as 82.8% and 87.9% in patients treated with cefepime and ceftazidime, respectively (P=0.94). Overall success rate of the empiric therapy was reported as 69% and 71% in patients treated with cefepime and ceftazidime, respectively (P=0.95). Bacteremic clearance was reported as 33% and 20% for patients treated with cefepime and ceftazidime, respectively (P=0.85). New infection rates were reported as 10.4% and 4.2% in patients treated with cefepime and ceftazidime, respectively (P=0.67). Secondary: Both treatments were well tolerated.
Jimeno et al.[127] (2006) Cefepime 2 g IV every 8 hours vs	RCT, SC Patients with solid tumors treated with high dose chemotherapy (HDC) and	N=51 episodes ≥4 days	Primary: Treatment success	Primary: The rate of success without treatment modifications were 14.8% and 55.5% in the combination and monotherapy arm, respectively (P=0.12). Major efficacy endpoints did not show significant differences, with success rates of 44.4% and 54.2% (P=0.481) for the combination arm and the monotherapy arm, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ceftazidime 2 g IV every 8 hours plus amikacin 500 mg IV every 12 hours	peripheral blood stem cell support (PBSCS) that developed fever and neutropenia (absolute neutrophil count < 500 cells/microL)			Among patients with fever of unknown origin cefepime was successful in 77.7% and ceftazidime plus amikacin was successful in 62.5% of episodes. The proportion of patients requiring treatment modifications was higher in the combination arm than in the monotherapy arm, but this difference did not reach statistical significance (85.2% vs 62.5%, P=0.120). The proportion of patients that became afebrile in the first 24 hours was significantly higher in the cefepime group (41.7% vs 11.1%, respectively; P= 0.012). There were seven episodes of antibiotic-related toxicity, two in the monotherapy arm and five in the combination arm. They consisted in mild and reversible elevations in serum creatinine, skin rash and mild hypokaliemia. Renal toxicity was related to the addition of vancomycin, and the addition of liposomal amphotericin B in the cefepime arm. In the ceftazidime plus amikacin arm it was related to the study combination and the addition of vancomycin.
Gómez et al.[139] (2010) Cefepime 2 g IV every 12 hours plus amikacin 15 mg/kg/day as a single dose (C-A) vs piperacillin-tazobactam 4 g/500 mg IV every 8 hours plus amikacin 15 mg/kg/day as a	RCT, OL Patients >18 years of age with an episode of febrile neutropenia	N=190 (317 episodes) Variable duration	Primary: Clinical efficacy and toxicity	Primary: The antibiotic success rate (no change or addition of antibiotics) was recorded in 59% of episodes in the C-A group and in 64% of episodes in the PT-A group (P=NS). Resolution of the febrile episode (with or without change in therapy) was observed in 92% of episodes in the C-A group and in 92% of episodes in the PT-A group. The 28-day mortality (all-cause) was similar in both groups: 9.9% in the C-A group and 10.5% in the PT-A group (P=NS). A microbiologically documented infection was present in 35% of episodes in the C-A group and 25% of episodes in the PT-A group (P=NS). A clinically documented infection was observed in 26% of episodes in the C-A group and 28% of episodes in the PT-A group.

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single dose (PT-A)				Toxicity was observed in 4% of episodes in the C-A group and in 3% of episodes in the PT-A group.
Pereira et al.[132] (2009) Cefepime 150 mg/kg/day administered 3 times daily (CFP) vs ceftriaxone 100 mg/kg/day administered twice daily plus amikacin 15 mg/kg/day (CFT+AK)	RCT, OL Patients ≤21 years of age with stage III-IV Hodgkin and non-Hodgkin lymphomas or acute leukemia who were admitted to the hospital with febrile neutropenia	N=57 (125 episodes) Variable duration	Primary: Therapeutic success	Primary: The initial treatment was modified in 41.9% of patients in the CFP group and 31.7% of patients in the CFT+AK group (P=0.23). The most frequently added drugs were amphotericin B and vancomycin. Treatment success was achieved in 65.5% of patients in the CFP group and 64.3% of patients in the CFT+AK group (P=0.92). Treatment failure was reported in 34.5% of patients in the CFP group and 35.7% of patients in the CFT+AK group (P=0.92). Success with treatment modification occurred in 93.0% of patients in the CFP group and 89.0% of patients in the CFT+AK group (P=0.60). Adverse events were reported in 16% of patients. The main adverse events were diarrhea, increased liver enzymes, headache and increased serum creatinine. One patient died in each group.
Uygun et al.[22] (2009) Cefepime 50 mg/kg IV every 8 hours (CEF) vs piperacillin-tazobactam 80 mg/kg-10 mg/kg IV every 6 hours (PIP/TAZO)	RCT, OL Patients ≤19 years of age who had been treated for hematological malignancies or solid tumors and had febrile neutropenia	N=70 (131 episodes) Variable duration	Primary: Success without modification	Primary: Success without modification was similar between the two groups (60.0% vs 61.3% for PIP/TAZO and CEF, respectively; P>0.05). Success without modification was 84.8% and 92.1% for PIP/TAZO and CEF treatments, respectively, in patients with fever of unknown origin (FUO) episodes. Success without modification was 29.2% and 12.5% in microbiologically documented infection episodes (P>0.05). Modifications were done with only glycopeptides in 8 episodes, only antifungals in 20 episodes, only carbapenems in 11 episodes, and only antiprotozoals in 2 episodes. Duration of fever and neutropenia was similar in both groups. There was no significant difference in the duration of hospitalization between the treatment groups.

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				No treatment changes were made because of potential side or adverse effect of PIP/TAZO or CEF. The most frequent adverse events were rash (7.7% in PIP/TAZO and 6.4% in CEF) and diarrhea (6.1% in PIP/TAZO and 6.4% in CEF).
LeFrock et al.[106] (1982) Cefotaxime 2 to 6 g/day IV	PRO Patients aged 15 to 91 years with serious bone and joint infections including septic arthritis, bursitis, acute/chronic osteomyelitis	N=51 4 to 54 days	Primary: Clinical response Secondary: Adverse events	Primary: Satisfactory clinical response was reported in 39 of 51 patients; clinical failure was reported in 6 patients. Secondary: Cefotaxime therapy was well tolerated with transient adverse events.
Mauceri et al.[107] (1994) Cefotaxime 1 g (moderate infections) to 2 g (severe infections) IV TID using an ambulatory delivery system	MC, OL, PRO Patients ≥18 years of age with bone and joint infections using an ambulatory delivery system for medication	N=18 30.5±17.52 days	Primary: Clinical response, bacteriological response Secondary: Adverse events	Primary: Satisfactory clinical response was reported in 83.8% of patients; satisfactory bacteriological response was reported in 78.6% of patients. All patients were eventually maintained on outpatient therapy. Secondary: Both the medication and delivery system were well tolerated. Two patients reported drug-related rash and one patient reported drug-related diarrhea.
Segev et al.[113] (1988) Cefotaxime 1 to 2 g IV TID vs ceftizoxime 1 to 2 g IV TID	MC, PRO, RCT Patients ≥17 years of age with moderate to severe infections	N=96 4 to 21 days	Primary: Clinical efficacy, bacteriological eradication Secondary: Adverse events	Primary: For both treatment groups, clinical efficacy and bacteriological eradication were reported as 90% and 95%, respectively. Secondary: Adverse events were more commonly reported by patients treated with cefotaxime compared to ceftizoxime (13.5% vs 6.8%, respectively); superinfection was more common with ceftizoxime therapy compared to cefotaxime therapy (25% vs 19%, respectively).
Kobayashi et al.[142]	RCT	N=54	Primary:	Primary:

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(2009) Ceftazidime 100 mg/kg/day plus piperacillin-tazobactam 125 mg/kg/day divided into 4 doses (PIPC-TAZ+CAZ) vs ampicillin-sulbactam 150 mg/kg/day plus aztreonam 150 mg/kg/day divided into 4 doses (SBT-ABPC+AZT) Treatment was continued until completion of the appropriate course of therapy for a defined clinical or microbiologic infection.	Pediatric patients with hematologic disease and solid tumor with febrile neutropenia	(177 episodes) 120 hours	Treatment success	Success rates were 57.1% and 62.5% in the PIPC-TAZ+CAZ and SBT-ABPC+AZT groups, respectively (P=>0.05). There were 2 deaths in the PIPC-TAZ+CAZ group. The patients died within 48 hours from onset of the febrile episode. The success rates in episodes with absolute neutrophil counts <0.5x10^9/L at the end of treatment were 70.0% and 74.1% in the PIPC-TAZ+CAZ and SBT-ABPC+AZT groups, respectively, and the success rates in bacteremia episodes were 50% in both groups. The percentages of episodes with new infections were 25.7% and 20.3%, respectively. Duration of fever and antibiotic therapy did not differ between the groups, and no major adverse effects occurred in the study.
Kaplinsky et al.[40] (1994) Ceftriaxone 50 mg/kg IV over 20 minutes	OL, PRO, non-RCT Pediatric outpatients with fever and neutropenia while being treated with various myelosuppressive agents for different	N=41 7 days	Primary: Clinical response, medication adherence	Primary: Patients treated with ceftriaxone reported normalization of temperature within 2 to 4 days of treatment and resolution of neutropenia after about 10 days. Medication adherence to ceftriaxone regimens, by both patients and patients' parents, was rated excellent.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	malignancies			
Metallidis et al.[120] (2008) Ceftriaxone 4 g IV every 24 hours plus ciprofloxacin 400 mg IV twice daily vs ceftazidime 2 g IV every 8 hours plus amikacin 500 mg IV every 8 hours or 20 mg/kg divided in three doses	RCT Patients with febrile neutropenia	N=95 ≥3 days	Primary: Microbiologically and clinically documented infections and adverse events	Primary: The overall incidence of microbiologically and clinically documented infections was 81.3% (80.85% in the ceftriaxone/ciprofloxacin group and 82.14% in the ceftazidime/amikacin group). There was no significant difference between the groups. The overall incidence of documented infections was 45.9% (51.1% in the ceftriaxone/ciprofloxacin group and 37% in the ceftazidime/amikacin group; P=0.011). The ceftriaxone/ciprofloxacin group had an overall incidence of resolution and improvement of 95.7% in comparison to 75% in the ceftazidime/amikacin group. Thirty-nine organisms were isolated, 66.67% gram-negative and 33.33% gram-positive. There was a low incidence of adverse events in both groups.
Bradley et al.[41] (1988) Ceftriaxone 50 mg/kg IV/IM QD (for non central nervous system infections) or ceftriaxone 100 mg/kg IV for day 1, then 80 mg/kg IV QD or BID (for meningitis)	PRO Pediatric outpatients aged 1 week to 15 years with serious bacterial soft tissue infections (egg cellulitis, arthritis, pyelonephritis) or meningitis using home therapy	N=101 1 to 6 days	Primary: Clinical failure, microbiologic failure Secondary: Adverse events	Primary: No clinical or microbiologic failures were reported in treatment groups. Pediatric patients with meningitis who were treated as outpatients did not report any neurologic dysfunction, cardiovascular instability, or relapse. Secondary: Diarrhea was reported in 13% and 6% of patients treated for meningitis and soft tissue infections, respectively. There were no discontinuations of therapy.
Dagan et al.[108] (1987)	PRO	N=74	Primary: Clinical response	Primary: A 24-hour cure rate was reported for 72 patients (97%) treated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ceftriaxone 75 mg/kg IM QD, then 50 mg/kg (maximum 1.5 g/day)	Pediatric out-patients aged 8 days to 17 years with serious community-acquired infection, including periorbital/buccal cellulitis, other cellulitis, urinary tract infection, pneumonia, osteomyelitis, mastoiditis, suppurative arthritis, orbital cellulitis	3 to 21 days	Secondary: Adverse events	ceftriaxone in the outpatient setting. Three cases of new infection were reported within 2 months post ceftriaxone therapy. Secondary: No serious adverse events were reported. The most commonly reported side effect was mild diarrhea which occurred in 10% of patients.
Dattwyler et al.[114] (1997) Ceftriaxone 2 g or 50 mg/kg IV QD (for 14 days) vs doxycycline 100 mg PO BID (for 21 days)	MC, OL, PRO, RCT Patients with acute disseminated *B burgdorferi* infection but without meningitis	N=140 14 to 21 days	Primary: Clinical cure, microbiologic cure Secondary: Adverse events	Primary: Clinical cure was reported as 85% and 88% in patients treated with ceftriaxone and doxycycline, respectively (P=NS). Microbiologic cure, despite residual symptoms, was reported as 27% and 14% in patients treated with ceftriaxone and doxycycline, respectively (P>0.05). Secondary: Both treatment regimens were well tolerated (P=0.128). The most commonly reported adverse event was mild arthralgia.
Huminer et al.[115] (1999) Ceftriaxone IV QD vs other IV antibiotics administered 1-5	PRO Outpatients aged 20 to 37 years with infective endocarditis and with home intravenous antibiotic therapy	N=37 14 to 49 days	Primary: Clinical response, patient satisfaction	Primary: Ceftriaxone and vancomycin were the most commonly prescribed agents for treating infective endocarditis in the outpatient setting. Thirty-four (97%) patients were cured when treated for infectious endocarditis using home intravenous antibiotic therapy. Thirty-five (95%) patients reported satisfaction with this therapy. Two patients required valve replacement; six patients were rehospitalized. Mean duration of therapy was shortest when patients were treated with ceftriaxone compared to other antibiotic regimens (22 vs 25 to 34, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
times daily (vancomycin, cloxacillin, vancomycin/ gentamicin, ampicillin/gentamicin, penicillin G, and aztreonam/gentamicin)	regardless of native or prosthetic heart valve			
Arguedas et al.[124] (2009) Ceftriaxone 50 mg/kg/day as a single daily dose (13-17 years of age) or 50 mg/kg/day divided twice daily (3 months to 12 years of age) vs ertapenem 1 gm as a single dose (13-17 years of age) or 30 mg/kg/day divided twice daily (3 months to 12 years of age) The protocol allowed for a switch to an oral antibacterial agent	RCT, DB, AC Patients ≥3 months and <18 years of age with complicated urinary tract infections, skin and soft-tissue infections and community-acquired pneumonia requiring initial parenteral antibiotic therapy	N=404 7-14 days post-treatment	Primary: Incidence of clinical and laboratory drug-related serious adverse events (AEs) Secondary: Incidence of any drug-related AEs and any moderate-to-severe reactions at the parenteral infusion site	Primary: In each group, the mean duration of therapy (parenteral and oral antibiotic therapy) was 11 days and the median duration of parenteral therapy (ertapenem or ceftriaxone) was 4 days. Overall, 46.7% of the children had one or more clinical AEs during parenteral therapy. During the parenteral therapy period, 26.7% of ertapenem-treated children and 24.0% of ceftriaxone-treated children reported a drug-related clinical and/or laboratory AE (P=0.69). Secondary: The most common drug-related clinical AEs during parenteral therapy were diarrhea, infusion site pain, infusion site erythema and vomiting. Eighteen patients (5.9%) receiving ertapenem and 10 patients (10%) receiving ceftriaxone experienced diarrhea. Fifteen patients (5%) and 1 patient (1%) receiving ertapenem and ceftriaxone, respectively, experienced infusion site pain. Nine patients (3%) receiving ertapenem and 2 patients (2%) receiving ceftriaxone experienced infusion site erythema. Six patients (2%) receiving ertapenem and 2 patients (2%) receiving ceftriaxone experienced vomiting. The most common laboratory AE in both groups was a decrease in the neutrophil count (5.7% in the ertapenem group and 2.2% in the ceftriaxone group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
after a minimum of 3 days of parenteral therapy.				In the ertapenem group, 18.8% of patients experienced more than one symptom at the site of drug administration during parenteral therapy of any intensity. The rates of moderate-to-severe local symptoms were comparable between the treatment groups (5.3% in the ertapenem group and 5.0% in the ceftriaxone group; P=1.000). The most common infusion/injection-related events were local erythema and pain. A total of 4.6% of children in the ertapenem group and 3.0% of children in the ceftriaxone group experienced erythema. A total of 6.6% of children in the ertapenem group and 4.0% of children in the ceftriaxone group experienced administration site pain.
Feurle et al.[134] (2010) Ceftriaxone 2 g IV once daily for 14 days followed by oral trimethoprim-sulfamethoxazole for 12 months vs meropenem 1 g 3 times daily for 14 days followed by oral trimethoprim-sulfamethoxazole for 12 months	RCT, OL Patients with previously untreated Whipple's disease	N=42 Variable duration	Primary: Maintenance of remission	Primary: After 3 months, all patients were in clinical and laboratory remission. After 12 months, the intestinal PAS-positive macrophages of all patients showed evidence of regression from subtype 1 to subtype 3. After a mean follow-up time of 41.5 months, intestinal biopsies in the ceftriaxone group revealed no or only a few scattered PAS-positive macrophages in 17 of 18 patients. The corresponding result in the meropenem group was no or a few PAS-positive macrophages in 17 of 18 patients after a mean follow-up period of evaluation of 39.8 months. The residual macrophages were of type 3, rarely type 4. In all patients, clinical, laboratory, and histopathologic remission was maintained at least up to the time of the last endoscopy, performed approximately 40 months after initial treatment.
Gupta et al.[23] (2009) Ceftriaxone 75 mg/kg/day IV and amikacin 15 mg/kg	RCT, SC, OL Pediatric patients 2 to 15 years of age with low-risk febrile neutropenia (LRFN)	N=88 (123 episodes) Variable duration	Primary: Treatment success	Primary: In the per protocol analysis, treatment was successful in 90.16% of episodes in the oral group and in 93.10% of episodes in the intravenous group. In the ITT analysis, the success rate was 88.7% in the oral group and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
once daily as outpatient therapy vs ofloxacin 7.5 mg/kg orally every 12 hours and amoxicillin-clavulanate 12.5 mg/kg orally every 8 hours as outpatient therapy				88.5% in the intravenous group (P=0.97). There were 3 hospitalizations (all in the oral group) and no mortality.
Solomkin et al.[141] (2009) Ceftriaxone 2 g IV once daily plus metronidazole 500 mg IV twice daily for 3 to 14 days vs moxifloxacin 400 mg IV once daily for 3 to 14 days	RCT, DB, MC Patients ≥18 years of age with community-origin complicated intra-abdominal infections (cIAIs) with an expected duration of treatment with IV antimicrobials of 3-14 days	N=364 Up to 28 days	Primary: Clinical success rate at the test-of-cure (TOC) visit (10 to 14 days after the end of therapy) Secondary: Clinical and bacteriological success rates on days 3 and 5 during treatment and at the end-of-therapy (EOT); bacteriological success rate at the TOC visit; and clinical success rate at the TOC visit in patients with bacteriologically proven cIAI	Primary: At the TOC visit, cure rates were 90.2% for moxifloxacin and 96.5% for ceftriaxone/metronidazole (95% CI, −11.7 to −1.7). In the ITT population, the clinical cure rates were 87.2% for moxifloxacin and 91.2% for ceftriaxone/metronidazole (95% CI, −10.7 to 1.9). Moxifloxacin was found to be non-inferior to ceftriaxone/metronidazole in the PP and ITT populations. Secondary: During treatment, clinical improvement occurred in similar proportions of PP patients in the moxifloxacin group (31.0%) and the ceftriaxone/metronidazole group (28.1%). In the ITT population, clinical improvement occurred in 30.6% of patients receiving moxifloxacin and 27.1% of patients receiving ceftriaxone/metronidazole. In the per protocol population, clinical resolution at EOT occurred in 92.5% of patients receiving moxifloxacin and in 97.1% of patients receiving ceftriaxone/metronidazole (95% CI, −9.8 to −0.2). In the ITT population, clinical resolution at EOT occurred in 91.1% of patients receiving moxifloxacin and in 94.5% of patients receiving ceftriaxone/metronidazole. Bacteriological success rates were comparable between treatment groups. The bacteriological success rates in the MBV population at TOC support

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the clinical results of moxifloxacin vs ceftriaxone/metronidazole (89.4% vs 95.9%, respectively; 95% CI, −13.3 to −0.6). The overall incidence of treatment-emergent AEs was similar between the two treatment groups (31.7% with moxifloxacin vs 24.3% with ceftriaxone/metronidazole; P=0.129).
Towfigh et al.[128] (2010) Ceftriaxone 2 g IV once daily plus metronidazole 1 to 2 g IV daily in divided doses for 4 to 14 days (CTX/MET) vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours for 4 to 14 days (TGC)	RCT, MC, OL Patients ≥18 years of age with community-origin complicated intra-abdominal infections (cIAIs)	N=473 Up to 35 days	Primary: Clinical response in the clinically evaluable (CE) population at the test-of-cure (TOC) visit Secondary: Bacteriological efficacy and safety	Primary: In the CE population, clinical cure was reported in 70% of patients receiving TGC and in 74% of patients in the CTX/MET group (-4.0; 95% CI, -13.1 to 5.1; P=0.009). TCG was found to be non-inferior to CTX/MET. Secondary: Clinical cure rates for the ME population were 66% with TGC and 70% with CTX/MET (-3.4; 95% CI, -14.5 to 7.8; P=0.020. TCG was found to be non-inferior to CTX/MET. In the c-mITT population, clinical cure was reported in 64% of patients receiving TGC and in 71% of patients receiving CTX/MET (-7.0; 95% CI, -15.8 to 1.08; P=0.038. TGC was found to be non-inferior to CTX/MET. *Escherichia coli* and *Bacteroides fragilis* were the most commonly isolated bacteria. For the ME population, clinical cure rates for the different pathogens were similar between the two treatment groups. At TOC in the ME population, infections were cured in 68.0% and 67.0% of all monomicrobial and polymicrobial infections, respectively, in the TGC-treated patients, and 71.5% and 68.3% of all monomicrobial and polymicrobial infections, respectively, in the CTX/MET-treated patients. Adverse events were similar with TGC and CTX/MET. There were no significant differences in the incidence of patients reporting one or more SAEs among the treatment groups (P=1.000). The most frequently reported SAEs overall were abscess (6.6%), infection (1.5%), respiratory failure (1.5%), abdominal pain (1.3%) and ileus (1.3%).
Song et al.[118] (1998)	MA Meta-analysis of	147 trials 12 years	Primary: Rate of surgical wound infections	Primary: There was no significant difference in the rate of surgical wound infections between many different regimens.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cefuroxime plus metronidazole vs gentamicin plus metronidazole vs first generation or second generation cephalosporin vs third generation cephalosporin vs other antibiotic agents as monotherapy or combination therapy	147 relevant randomized controlled trials published between 1984 and 1995			However, certain regimens appeared to be inadequate (e.g., metronidazole alone, doxycycline alone, piperacillin alone, oral neomycin plus erythromycin on the day before operation). A single dose administered immediately before the operation (or short-term use) was judged as effective as long-term postoperative antimicrobial prophylaxis (OR=1.17 [95% CI: 0.90 to 1.53]). There is no convincing evidence to suggest that the new-generation cephalosporins are more effective than first generation cephalosporins (OR 1.07, 95% CI: 0.54 to 2.12).
Chen et al.[125] (2011) Cephalexin 40 mg/kg/day orally in divided doses 3 times per day for 7 days vs	RCT Patients 6 months to 18 years of age with uncomplicated skin and soft tissue infections (SSTIs) not requiring hospitalization	N=200 3 months	Primary: Clinical improvement at 48 to 72 hours from the initiation of treatment Secondary: Resolution of disease at 7 days	Primary: A total of 94% of patients in the cephalexin group and 97% of patients in the clindamycin group showed improvement or resolution in their infection at 48 to 72 hours from the initial of treatment (P=0.50). The primary infection had worsened in 6% of patients in the cephalexin group and in 3% of patients in the clindamycin group. Secondary: A total of 97% of patients in the cephalexin group and 94% of patients in the clindamycin group had clinical resolution by 7 days (P=0.33). Only 1 patient developed a new SSTI while on therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clindamycin 20 mg/kg/day orally in divided doses 3 times per day for 7 days				Compliance with taking medications as directed was 88% in the cephalexin group and 85% in the clindamycin group (P=0.66). According to data obtained from telephone contact (73%) and chart review (100%) at the 3-month follow-up, 18% of patients had a recurrent SSTI. The risk of new SSTI did not differ according to isolation of MRSA vs MSSA from initial wound culture (21% MRSA vs 16% MSSA; P=0.51) or by cephalexin or clindamycin assignment (20% vs 16%; P=0.46). There were no serious adverse events related to study treatment.

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily, IM=intramuscularly, IV=intravenously, PO=by mouth
Study abbreviations: AC=active-controlled, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RETRO=retrospective, RCT=randomized controlled trial, SB=single-blind, XO=crossover

Additional Evidence

Dose Simplification:
Frequency of dosing is identified as a major factor in compliance for antibiotic treatment.[119] Average compliance is reduced as dosing frequency is increased. Acceptable compliance was observed most frequently with once or twice daily antibiotic regimens.[119] In a study of medication adherence, Ballantyne reported no significant difference in clinical efficacy for patients treated with once daily cefadroxil compared to cefaclor administered three times daily (91% vs 95%, respectively; P=0.41). However, medication adherence was greater in patients treated with cefadroxil once daily compared to patients treated with cefaclor three times daily (2% vs 77%, respectively).[98]

A study comparing intramuscular ceftriaxone (for up to 2 doses) and oral amoxicillin-clavulanate (three times daily for 10 days) in patients with acute otitis media demonstrated similar treatment failure rates in both groups (4.6% and 4.7%, respectively).[72] However, recurrence rates of acute otitis media between days 31 and 90 were observed significantly more frequently in children treated with amoxicillin-clavulanate than with ceftriaxone (29.4% vs 13.6%; P=0.012). Seventy-five percent of study participants took amoxicillin-clavulanate as prescribed or in excess; 25% of study participants took amoxicillin-clavulanate in a quantity less than that prescribed. More parents preferred the intramuscular route over oral therapy (68% vs 32%, respectively; P=0.0001).

Stable Therapy:
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 13. Relative Cost of the Cephalosporins

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Cefaclor	capsule, extended-release tablet	N/A	N/A	$$-$$$$
Cefadroxil	capsule, suspension, tablet	N/A	N/A	$-$$$
Cefazolin	injection	N/A	N/A	$-$$$$
Cefdinir	capsule, suspension	N/A	N/A	$$-$$$
Cefditoren	tablet	Spectracef®*	$$$$$	$$$$$
Cefepime	injection	N/A	N/A	$$$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Cefixime	suspension, tablet	Suprax®	$$$$-$$$$$	N/A
Cefotaxime	injection	Claforan®*	$$-$$$$$	$-$$$
Cefpodoxime	suspension, tablet	N/A	N/A	$$-$$$
Cefprozil	suspension, tablet	N/A	N/A	$-$$$
Ceftaroline	injection	Teflaro®	$$$$$	N/A
Ceftazidime	injection	Fortaz®*, Fortaz in Iso-Osmotic Dextrose®, Tazicef®*	$$$-$$$$$	$$$-$$$$$
Ceftibuten	capsule, suspension	Cedax®	$$$$-$$$$$	N/A
Ceftriaxone	injection	Rocephin®*	$$$-$$$$$	$-$$$$$
Cefuroxime	injection, suspension, tablet	Ceftin®*, Zinacef®*, Zinacef in Iso-Osmotic Dextrose®, Zinacef in Iso-Osmotic Water®	$$$$-$$$$$	$-$$$
Cephalexin	capsule, suspension, tablet	Keflex®*	$$$-$$$$$	$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The cephalosporins are approved to treat a variety of infections, including central nervous system, dermatologic, genitourinary, respiratory, as well as several miscellaneous infections.[1-13] They are often grouped into generations according to their spectrum of activity. The majority of the cephalosporins are available in a generic formulation. There is at least one oral and one injectable agent available in a generic formulation within each cephalosporin generation, with the exception of cefepime and ceftaroline.

There are many guidelines that define the appropriate place in therapy for the cephalosporins. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the cephalosporin. The cephalosporins are recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, encephalitis, meningitis, skin and soft-tissue infections, infectious diarrhea, sexually transmitted diseases, infectious exacerbations of COPD, nosocomial pneumonia, febrile neutropenia, intra-abdominal infections, Lyme disease, and for surgical prophylaxis.[15-16,18,20-21,31,34-35,37-39,143-144,147-149] They are recommended as an alternative treatment option for urinary tract infections, otitis media, group A streptococcal pharyngitis, community-acquired pneumonia, and sinusitis, especially in situations where the patient is allergic to penicillin.[19,25-30,36,145]

Numerous studies have demonstrated comparable efficacy among the cephalosporins for the treatment of skin and soft-tissue infections, urinary tract infections, upper/lower respiratory tract infections, febrile neutropenia, and for surgical prophylaxis.[42-52,57,59,61-64,76-85,89,94-95,98-101,109-112,116,122-123,126-127,132] There are relatively few studies which demonstrate greater clinical cure or microbiological eradication rates with one cephalosporin over another.[55,58,60,86,88,104-105,120] Data from published studies supports similar safety profiles among the cephalosporins, particularly within each generation.

Ceftaroline is approved for the treatment of skin and skin-structure infections, as well as community-acquired pneumonia.[7] Two studies compared ceftaroline to the combination of vancomycin and aztreonam in patients with complicated skin and skin-structure infections.[130-131,137] Clinical cure rates were similar among the treatment groups in the clinically evaluable and modified intent-to-treat populations, as well as in patients infected with methicillin-resistant *Staphylococcus aureus*. Two studies compared ceftaroline to ceftriaxone in patients with community-acquired pneumonia.[135-136,138] Ceftaroline was found to be non-inferior to ceftriaxone in the clinically evaluable population.

There is insufficient evidence to support that one brand cephalosporin is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand cephalosporins within the class reviewed are comparable to each other and to the generics, within each cephalosporin generation, and OTC products (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand cephalosporin is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2011. Available from Wolters Kluwer Health, Inc. Accessed October 2011.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2011; October 2011.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed October 2011.
4. Spectracef® [package insert]. Cary, NC: Cornerstone Therapeutics, Inc.; September 2009.
5. Suprax® [package insert]. Baltimore, MD: Lupin Pharmaceuticals, Inc.; October 2008.
6. Claforan® [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC; September 2011.
7. Teflaro® [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; April 2011.
8. Fortaz® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; August 2010.
9. Cedax® [package insert]. Florham Park, NJ: Schiongi USA, Inc.; April 2008.
10. Rocephin® [package insert]. South San Francisco, CA: Genentech USA, Inc.; November 2010.
11. Ceftin® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; January 2010.
12. Zinacef® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; August 2010.
13. Keflex® [package insert]. Germantown, MD: Advancis Pharmaceutical Corp.; March 2006.
14. Calderwood SB. Cephalosporins. In: UpToDate, Baron, EL (Ed), UpToDate, Waltham, MA, 2011.
15. Chaudhuri A, Martinez-Martin P, Kennedy PG, Andrew Seaton R, Portegies P, Bojar M, Steiner I; EFNS Task Force. EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. Eur J Neurol 2008;15:649-59.
16. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1-110.
17. Rosenfeld R, Andes D, Bhattacharyya N, et al. American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF). Clinical practice guideline: adult sinusitis. Otolaryngol Head Neck Surg 2007;137(Suppl 3):S1-31.
18. American Thoracic Society and the Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388–416.
19. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 91: Treatment of urinary tract infections in nonpregnant women. Obstet Gynecol 2008;111:785-94.
20. Tunkel AR, Hartman BJ, Kaplan SL, et al. Infectious Diseases Society of America. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267-84.
21. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR, Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:e56-93.
22. Uygun V, Karasu GT, Ogunc D, et al. Piperacillin/tazobactam versus cefepime for the empirical treatment of pediatric cancer patients with neutropenia and fever: a randomized and open-label study. Pediatr Blood Cancer 2009;53:610-4.
23. Gupta A, Swaroop C, Agarwala S, et al. Randomized controlled trial comparing oral amoxicillin-clavulanate and ofloxacin with intravenous ceftriaxone and amikacin as outpatient therapy in pediatric low-risk febrile neutropenia. J Pediatr Hematol Oncol 2009;31:635-41.
24. Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis 2005;40:643-54.
25. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatr. 2004 May;113(5):1451-65.
26. Slavin R, Spector S, Bernstein IL, et al; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol. 2005;116(6):S13-S47.
27. American Academy of Pediatrics subcommittee on the management of sinusitis and committee on quality improvement. Clinical practice guideline: management of sinusitis. Pediatrics. 2001;108(3):798-808.
28. Bisno A, Gerber M, Gwaltney J, et al. Practice guideline for the diagnosis and management of group A Streptococcal pharyngitis. Clin Infect Dis. 2002;35(2):113-25.

29. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-S72.
30. Ramsdell J, Narsavage GL, Fink JB; American College of Chest Physicians' Home Care Network Working Group. Management of community-acquired pneumonia in the home: an American College of Chest Physicians clinical position statement. Chest 2005;127:1752-63.
31. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2010. 117 p. Available at: www.goldcopd.com. Accessed October 2011.
32. Braman SS. Chronic cough due to chronic bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129 (1 Suppl): 104S-15S.
33. Braman SS. Chronic cough due to acute bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129 (1 Suppl): 95S-103S.
34. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005 Nov 15;41(10):1373-406.
35. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50:133-64.
36. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20.
37. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis. 2004;38:1706–15.
38. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. Circulation. Jun 2005;111:e394-e434.
39. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis. Clin Infect Dis. 2006;43:1089–134.
40. Kaplinsky P, Drucker M, Goshen J, et al. Ambulatory treatment with ceftriaxone in febrile neutropenic children. Isr J Med Sci. 1994;30:649-51.
41. Bradley JS, Ching DK, Phillips SE. Outpatient therapy of serious pediatric infections with ceftriaxone. Pediatr Infect Dis J. 1988;7(3):160-4.
42. Chandrasekar PH, Arnow PM. Cefepime versus ceftazidime as empiric therapy for fever in neutropenic patients with cancer. Ann Pharmacother. 2000;34:989-95.
43. Chuang YY, Hung IJ, Yang CP, et al. Cefepime versus ceftazidime as empiric monotherapy for fever and neutropenia in children with cancer. Pediatr Infec Dis J. 2002;21:203-9.
44. Leigh AP, Nemeth MA, Keyserling CH, et al. Cefdinir versus cefaclor in the treatment of uncomplicated urinary tract infection. Clin Ther. 2000;22(7):818-25.
45. Christenson JC, Gooch WM, Herrod JN, et al. Comparative efficacy and safety of cefprozil and cefaclor in the treatment of acute uncomplicated urinary tract infections. J Antimicrob Chemother. 1991;28:581-6.
46. Bolding OT. Comparison of the efficacy and safety of cefadroxil and cephalexin in treating acute urinary tract infections in woman. J Int Med Res. 1980;8(Suppl. 1): 34-9.
47. Madsen PO, Iversen P. Cefotaxime and cefazolin in the treatment of complicated urinary tract infections: a comparative study. Clin Ther. 1981;4(1):7-11.
48. Sanchez-Ramos L, McAlpine KJ, Adair CD, et al. Obstetrics: pyelonephritis in pregnancy: once-a-day ceftriaxone versus multiple doses in cefazolin: a randomized, double-blind trial. Am J Obstet Gynecol. 1995;172(1):129-33.
49. Iversen P, Madsen PO. Complicated urinary tract infections treated with cefuroxime or cefazolin: a comparative study. Clin Ther. 1981;4(4):302-7.
50. Newton ER, Yeomans ER, Pastorek JG, et al. Randomized comparative study of cefepime and cefotaxime n the treatment of acute obstetric and gynaecological infections. J Antimicrob Ther. 1993;32:195-204.

51. Gentry LO, Rodriguez-Gomez G. Randomized comparison of cefepime and ceftazidime for treatment of skin, surgical wound, and complicated urinary tract infection in hospitalized subjects. Antimicrob Agents Chemother. 1991;35(11):2371-4.
52. Ho MW, Wang FD, Fung CP, et al. Comparative study of ceftibuten and cefixime in the treatment of complicated urinary tract infections. J Microbiol Immunol Infect. 2001;34:185-9.
53. Tripi M, Pavone-Macaluso M, Giammanco A, et al. Randomized comparative trial with cefizoxime and cefotaxime in urinary tract infections. Int Urol Nephrol. 1985;17(3):195-202.
54. Goldstein AMB, Clark JH, Wickler MA. Comparison of single-dose ceftizoxime or ceftriaxone in the treatment of uncomplicated urethral gonorrhea. Sex Transm Dis. 1991;18(3):180-2.
55. Cooper J, Raeburn A, Brumfitt W, et al. Comparative efficacy and tolerability of cephradine and cefuroxime axetil in the treatment of acute dysuria and/or frequency in general practice. Br J Clin Pract 1992;46:24-7.
56. Aplasca de los Reyes MR, Pato-Mesola V, Klausner JD, et al. A randomized trial of ciprofloxacin versus cefixime for treatment of gonorrhea after rapid emergence of gonococcal ciprofloxacin resistance in the Phillipines. CID. 2001;32:1313-8.
57. Arrieta AC, Bradley JS. Empiric use of cefepime in the treatment of serious urinary tract infections in children. Pediatr Infect Dis. 2001;20:350-5.
58. Randolph MF. Clinical comparison of once-daily cefadroxil and thrice daily cefaclor in the treatment of streptococcal pharyngitis. Chemother. 1988;34:512-8.
59. Piippo T, Stefansson S, Pitkajarvi T, et al. Double-blind comparison of cefixime and cefaclor in the treatment of acute otitis media in children. Scand J Infect Dis. 1991;23:459-65.
60. Gehanno P, Depondt J, Barry B, et al. Comparison of cefpodoxime proxetil with cefaclor in the treatment of sinusitis. J Antimicrob Chemother. 1990;26(Suppl E): 87-91.
61. MacLoughlin GJF, Barreto DG, Torre C, et al. cefpodoxime proxetil suspension compared with cefaclor suspension for treatment of acute otitis media in paediatric patients. J Antimicrob Chemother 1996;37:565-73.
62. Blumer JL, McLinn SE, Deabate A, et al. Multinational multicenter controlled trial comparing ceftibuten with cefaclor for the treatment of acute otitis media. Pediatr Infect Dis J. 1995;14:S115-20.
63. Block SL, Kratzer J, Nemeth MA, et al. Five-day cefdinir course vs ten-day cefprozil course for treatment of acute otitis media. Pediatr Infect Dis J. 2000;19(12):S147-S52.
64. Asmar BS, Dajani AS, Del Beccaro, et al. Comparison of cefpodoxime proxetil and cefixime in the treatment of acute otitis media in infants and children. Pediatrics. 1994;94(6):847-52.
65. Milatovic D, Knauer J. Cefadroxil versus penicillin in the treatment of streptococcal tonsillopharyngitis. Eur J Clin Microbiol. 1989;8(4):282-8.
66. Gwaltney JM, Savolainen S, Rivas P, et al. Comparative effectiveness and safety of cefdinir and amoxicillin-clavulanate in treatment of acute community-acquired bacterial sinusitis. Antimicrob Agents Chemother. 1997;41(7):1517-20.
67. Brook I. A pooled comparison of cefdinir and penicillin in the treatment of group A beta-hemolytic streptococcal pharyngotonsillitis. Clin Ther. 2005;27(8):1266-1273.
68. Mendelman PM, Del Beccaro MA, McLinn SE, et al. Cefpodoxime proxetil compared with amoxicillin-clavulanate for the treatment of otitis media. Pediatr Pharmacol Ther. 1992;121(3):459-65.
69. Pichichero ME, Gooch WM, Rodriguez W, et al. Effective short-course treatment of acute group A beta-hemolytic streptococcal tonsillopharyngitis. Arch Pediatr Adolesc Med. 1994;148:1053-60.
70. Adelglass J, Bundy JM, Woods R. Efficacy and tolerability of cefprozil versus amoxicillin/clavulanate for the treatment of adults with severe sinusitis. Clin Ther. 1998;20(6):1115-29.
71. Pichichero ME, McLinn SE, Gooch WM, et al. Ceftibuten vs penicillin V in group A beta-hemolytic streptococcal pharyngitis. Pediatr Infect Dis J. 1995;14(7):S102-S7.
72. Varsano I, Volovitz B, Horev Z, et al. Intramuscular ceftriaxone compared with oral amoxicillin-clavulanate for the treatment of acute otitis media in children. Eur J Pediatr. 1997;156:858-63.
73. Camacho AE, Cobo R, Otte J, et al. Clinical comparison of cefuroxime axetil and amoxicillin/clavulanate in the treatment of patients with acute bacterial maxillary sinusitis. Am J Med. 1992;93:271-6.
74. Aujard Y, Boucot I, Brahimi N, et al. Comparative efficacy and safety of four-day cefuroxime axetil and ten-day penicillin treatment of group A beta-hemolytic streptococcal pharyngitis in children. Pediatr Infect Dis J. 1995;14:295-300.
75. Disney FA, Dillon H, Blumer J, et al. Cephalexin and penicillin in the treatment of group A beta-hemolytic streptococcal throat infections. AJDC. 1992;146:1324-7.
76. McCarty JM. Comparative efficacy and safety of cefprozil versus penicillin, cefaclor and erythromycin in the treatment of streptococcal pharyngitis and tonsillitis. Eur J Clin Microbiol Infect Dis 1994;13:846-50.

77. ZeLuff B, Catchpole M, Lowe P, et al. Cefadroxil compared with cefaclor in the treatment of streptococcal pneumonia in adults. Drugs. 1986;32(Suppl. 3):39-42.
78. Drehobl M, Bianchi P, Keyserling CH, et al. Comparison of cefdinir and cefaclor in the treatment of community-acquired pneumonia. Antimicrob Agents Chemother. 1997;41(7):1579-83.
79. Phillips H, Van Hook CJ, Butler T, et al. A comparison of cefpodoxime proxetil and cefaclor in the treatment of acute exacerbation of COPD in adults. Chest. 1993;104(5):1387-91.
80. Chirurgi VA, Edelstein H, Oster SE, et al. Ceftibuten versus cefaclor for the treatment of bronchitis. J Antimicrob Chemother. 1991;28:577-80.
81. Blaser MJ, Klaus BD, Jacobson JA, et al. Comparison of cefadroxil and cephalexin in the treatment of community-acquired pneumonia. Antimicrob Agents and Chemother. 1983;24(2):163-7.
82. Fogarty CM, Bettis RB, Griffin TJ, et al. Comparison of a 5 day regimen of cefdinir with a 10 day regimen of cefprozil for treatment of acute exacerbation of chronic bronchitis. J Antimicrob Chemother. 2000;45:851-8.
83. Alvarez-Sala JL, Kardos P, Martinez-Beltran J, et al. Clinical and bacteriological efficacy in treatment of acute exacerbations of chronic bronchitis with cefditoren-pivoxil versus cefuroxime-axetil. Antimicrob Agents Chemothera. 2006;50(5):1762-7.
84. Leophonte P, Bertrand A, Nouvet G, et al. A comparative study of cefepime and ceftazidime in the treatment of community-acquired lower respiratory tract infections. J Antimicrob Chemother 1993;31:165-73.
85. Grossman RF, Campbell DA, Landis SJ, et al. Treatment of community-acquired pneumonia in the elderly: the role of cefepime, a fourth generation cephalosporin. J Antimicrob Chemother. 1999;43:549-54.
86. Verghese A, Roberson D, Kalbfleisch JH, et al. Randomized comparative study of cefixime versus cephalexin in acute bacterial exacerbations of chronic bronchitis. Antimicrob Agents Chemother. 1990;34(6):1041-4.
87. Sengupta J, Mondal AK, Jain P, et al. Comparative evaluations of cefpodoxime versus cefixime in children with lower respiratory tract infections. Indian J Pediatr. 2004;71(6):517-21.
88. Zuck P, Pettipretz P, Rio Y, et al. Bacteriological eradication of streptococcus pneumoniae from patients with acute exacerbations of chronic bronchitis: cefuroxime axetil versus cefixime. Int J Clin Prac. 1999;53(6):437-43.
89. Fogarty CM, Cyganowski M, Palo WA, et al. A comparison of cefditoren pivoxil and amoxicillin/clavulanate in the treatment of community-acquired pneumonia: a multi-center, prospective, randomized, investigator-blinded, parallel-group study. Clin Ther. 2002;24(11):1854-70.
90. McAdoo MA, Rice K, Gordon GR, et al. Comparison of ceftibuten once daily and amoxicillin-clavulanate three times daily in the treatment of acute exacerbations of chronic bronchitis. Clin Ther. 1998;20(1):88-100.
91. Ziering W, McElvaine P. Randomized comparison of once-daily ceftibuten and twice daily clarithromycin in the treatment of acute exacerbations of chronic bronchitis. Infection 1998;26(1):68-75.
92. Brambilla C, Kastanakis S, Cunningham K. Cefuroxime and cefuroxime axetil versus amoxicillin plus clavulanic acid in the treatment of lower respiratory tract infections. Eur J Clin Microbiol Infect Dis. 1992;11(2):118-24.
93. Henry D, Ruoff GE, Rhudy J, et al. Effectiveness of short-course therapy (5 days) with cefuroxime axetil in treatment of secondary bacterial infections of acute bronchitis. Antimicrob Agents Chemother. 1995;39(11):2528-34.
94. Ball P. Efficacy and safety of cefprozil versus other beta-lactam antibiotics in the treatment of lower respiratory tract infections. Eur J Clin Microbiol Infect Dis. 1994;13(10): 851-6.
95. Bradley JS, Arrieta A. Empiric use of cefepime in the treatment of lower respiratory tract infections in children. Pediatr Infect Dis J. 2001;20:343-9.
96. Leder K, Turnidge JD, Grayson ML. Home-based treatment of cellulitis with twice daily cefazolin. MJA. 1998;169:519-22.
97. Eron LJ, Park CH, Hixon DL, et al. Ceftriaxone therapy of bone and soft tissue infections in hospital and outpatient settings. Antimicrob Agents and Chemother. 1983;23(5):731-7.
98. Ballantyne FN. Comparative efficacy of cefadroxil and cefaclor in the treatment of skin and soft-tissue infections. Clin Ther. 1985;7(4):487-91.
99. Stevens DL, Pien F, Drehobol M. Comparison of oral cefpodoxime proxetil and cefaclor in the treatment of skin and soft tissue infections. Diagn Microbiol Infect Dis. 1993;16:123-9.
100. Ballantyne F. A comprehensive study of cefadroxil and cephalexin in the treatment of soft tissue infections. J International Med Res 1980;8(Suppl. 1): 70-4.
101. Tack KJ, Keyserling CH, McCarty J, et al. Study of use of cefdinir versus cephalexin for treatment of skin infections in pediatric patients. Antimicrob Agents and Chemother. 1997;41(4):739-42.

102. Gentry LO, Ramirez-Ronda CH, Rodriguez-Noriega E, et al. Oral ciprofloxacin vs parenteral cefotaxime in the treatment of difficult skin and skin structure infections. Arch Intern Med. 1989;149:2579-83.
103. Gentry LO, Koshdel A. Intravenous/oral ciprofloxacin versus intravenous ceftazidime in the treatment of serious gram-negative infections of the skin and skin structure. Am J Med. 1989;87(Suppl. 5A):132S-5S.
104. Bucko AD, Hunt BJ, Kidd SL, et al. Randomized, double-blind, multicenter comparison of oral cefditoren 200 or 400 mg BID with either cefuroxime 250 mg BID or cefadroxil 500 mg BID for the treatment of uncomplicated skin and skin-structure infections. Clin Ther. 2002;27(7):1134-47.
105. Gooch WM, Kaminester L, Cole GW, et al. Clinical comparison of cefuroxime axetil, cephalexin and cefadroxil in the treatment of patients with primary infections of the skin or skin structures. Dermatologica. 1991;183:36-43.
106. LeFrock JL, Carr BB. Clinical experience with cefotaxime in the treatment of serous bone and joint infections. Rev Infect Dis. 1982;4 Suppl:S465-71.
107. Mauceri AA. Treatment of bone and joint infections utilizing a third generation cephalosporin with an outpatient drug delivery device. Am J Med. 1994;97(Suppl 2A):14-22.
108. Dagan R, Phillip M, Watemberg, et al. Outpatient treatment of serious community-acquired infections using once daily intramuscular ceftriaxone. Pediatr Infect Dis J. 1987;6:1080-4.
109. Nungu KS, Olerud C, Rehnberg L, et al. Prophylaxis with oral cefadroxil versus intravenous cefuroxime in trochanteric fracture surgery: a clinical multicentre study. Arch Orthop Trauma Surg. 1995;114:303-7.
110. Curtis JJ, Boley TM, Walls JT, et al. Randomized, prospective comparison of first- and second generation cephalosporins as infection prophylaxis for cardiac surgery. Am J Surgery. 1993;166:734-58.
111. Jewesson PJ, Stiver G, Wai A, et al. Double-blind comparison of cefazolin and ceftizoxime for prophylaxis against infections following elective biliary tract surgery. Antimicrob Agents and Chemother. 1996;40(1):70-4.
112. Huang CK, Chen YS, Lee SSJ. Safety and efficacy of cefepime versus ceftazidime in the treatment of severe infections. J Microbiol Immunol Infect. 2002;35:159-67.
113. Segev S, Kitzes R, Rubinstein E, et al. Ceftizoxime vs cefotaxime – a comparative randomized multicenter study. Isr J Med Sci. 1988;24:410-4.
114. Dattwyler RJ, Luft BJ, Kunkel MJ, et al. Ceftriaxone compared with doxycycline for the treatment of acute disseminated Lyme disease. NEJM. 1997;337(5):289-94.
115. Huminer D, Bishara J, Pitlik S. Home intravenous antibiotic therapy for patients with infective endocarditis. Eur J Clin Infect Dis. 1999;18:330-4.
116. Jones RN, Wojeski W, Bakke J, et al. Antibiotic prophylaxis of 1,036 patients undergoing elective surgical procedures. Am J Surg. 1987;153:341-6.
117. Gentry LO, Rodriguez-Gomez G. Ofloxacin versus parenteral therapy for chronic osteomyelitis. Antimicrob Agents Chemother. 1991;35(3):538-41.
118. Song F, Glenny AM. Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomized controlled trials. Br J Surg 1998 Sep;85(9):1232-41.
119. Kardas P. Patient compliance with antibiotic treatment for respiratory tract infections. J Antimicrob Chemother. 2002;49:897-903.
120. Metallidis S, Kollaras P, Giannakakis T, et al. A prospective, controlled, randomized, non-blind, comparative study of the efficacy and safety of a once daily high dose of ceftriaxone plus ciprofloxacin versus thrice daily ceftazidime plus amikacin in empirical therapy for febrile neutropenic patients. Eur J Intern Med 2008;19:619-24.
121. Lewis KT, Stiles M. Management of cat and dog bites. Am Fam Physician. 1995;52:479-485,489-90.
122. Ozturk M, Koca O, Kaya C, et al. A prospective randomized and placebo-controlled study for the evaluation of antibiotic prophylaxis in transurethral resection of the prostate. Urol Int 2007;79:37-40.
123. Giordano P, Elston D, Akinlade B, et al. Cefdinir vs cephalexin for mild to moderate uncomplicated skin and skin structure infections in adolescents and adults. Curr Med Res Opin 2006;22:2419-28.
124. Arguedas A, Cespedes J, Botet FA, et al. Safety and tolerability of ertapenem versus ceftriaxone in a double-blind study performed in children with complicated urinary tract infection, community-acquired pneumonia or skin and soft-tissue infection. Int J Antimicrob Agents 2009;33163-7.
125. Chen AE, Carroll KC, Diener-West M, et al. Randomized controlled trial of cephalexin versus clindamycin for uncomplicated pediatric skin infections. Pediatrics 2011;127:e573-80.
126. Paladino J, Eubanks D, Adelman M, et al. Once-daily cefepime versus ceftriaxone for nursing home-acquired pneumonia. J Am Geriatr Soc 2007;55:651-7.

127. Jimeno A, Arcediano A, Bazares S, et al. Randomized study of cefepime versus ceftazidime plus amikacin in patients with solid tumors treated with high dose chemotherapy (HDC) and peripheral blood stem cell support (PBSCS) with febrile neutropenia. Clin Transl Oncol 2006;8:889-95.
128. Towfigh S, Pasternak J, Poirier A, et al. A multicentre, open-label, randomized comparative study of tigecycline versus ceftriaxone sodium plus metronidazole for the treatment of hospitalized subjects with complicated intra-abdominal infections. Clin Microbiol Infect 2010;16:1274-81.
129. Ziogos E, Tsiodras S, Matalliotakis I, et al. Ampicillin/sulbactam versus cefuroxime as antimicrobial prophylaxis for cesarean delivery: a randomized study. BMC Infect Dis 2010;10:341.
130. Corey GR, Wilcox MH, Talbot GH, et al. CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65 Suppl 4:iv41-51.
131. Wilcox MH, Corey GR, Talbot GH, et al. CANVAS 2: the second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65 Suppl 4:iv53-iv65.
132. Pereira CA, Petrilli AS, Carlesse FA, et al. Cefepime monotherapy is as effective as ceftriaxone plus amikacin in pediatric patients with cancer and high-risk febrile neutropenia in a randomized comparison. J Microbiol Immunol Infect 2009;42:141-7.
133. Mårild S, Jodal U, Sandberg T, et al. Ceftibuten versus trimethoprim-sulfamethoxazole for oral treatment of febrile urinary tract infection in children. Pediatr Nephrol 2009;24:521-6.
134. Feurle GE, Junga NS, Marth T. Efficacy of ceftriaxone or meropenem as initial therapies in Whipple's disease. Gastroenterology 2010;138:478-86.
135. File TM Jr, Low DE, Eckburg PB, et al. FOCUS 1: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. J Antimicrob Chemother 2011;66 Suppl 3:iii19-32.
136. Low DE, File TM Jr, Eckburg PB, et al. FOCUS 2: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. J Antimicrob Chemother 2011;66 Suppl 3:iii33-44.
137. Corey GR, Wilcox M, Talbot GH, et al. Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. Clin Infect Dis 2010;51:641-50.
138. File TM Jr, Low DE, Eckburg PB, et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. Clin Infect Dis 2010;51:1395-405.
139. Gómez L, Estrada C, Gómez I, et al. Low-dose beta-lactam plus amikacin in febrile neutropenia: cefepime vs piperacillin/tazobactam, a randomized trial. Eur J Clin Microbiol Infect Dis 2010;24:417-27.
140. Khawcharoenporn T, Tice A. Empiric outpatient therapy with trimethoprim-sulfamethoxazole, cephalexin, or clindamycin for cellulitis. Am J Med 2010;123:942-50.
141. Solomkin J, Zhao YP, Ma EL, et al. Moxifloxacin is non-inferior to combination therapy with ceftriaxone plus metronidazole in patients with community-origin complicated intra-abdominal infections. Int J Antimicrob Agents 2009;34:439-45.
142. Kobayashi R, Sato T, Nakajima M, et al. Piperacillin/tazobactam plus ceftazidime versus sulbactam/ampicillin plus aztreonam as empirical therapy for fever in severely neutropenic pediatric patients. J Pediatr Hematol Oncol 2009;31:270-3.
143. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Eur Heart J 2009;30:2369-413.
144. Bonow R, Carabello B, Chatterjee K et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e1-142.
145. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011;53:e25-76.

146. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52:1-38.
147. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, LeFrock JL, Lew DP, Mader JT, Norden C, Tan JS; Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004 Oct 1;39(7):885-910.
148. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM, Whitley RJ, Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303-27.
149. Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, et al; Infectious Diseases Society of America. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis. 2001;32:331-51.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Miscellaneous β-Lactam Antibiotics
AHFS Class 081207
February 8, 2012

I. Overview

The miscellaneous β-lactam antibiotics are approved to treat a variety of infections, including central nervous system, dermatologic, genitourinary, respiratory, as well as several miscellaneous infections.[1-10] With the exception of aztreonam inhalation solution, the miscellaneous β-lactam antibiotics are only available in an injectable formulation and are primarily administered in the inpatient setting. Aztreonam inhalation solution is approved to improve respiratory symptoms in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*.[5]

The β-lactam antibiotics exert their antibacterial activity by binding to penicillin-binding proteins, which inactivates the enzymes responsible for cell-wall synthesis in susceptible microorganisms. Aztreonam belongs to the monobactam class of antibiotics and has strong activity against susceptible gram-negative bacteria; however, it has no useful activity against gram-positive bacteria or anaerobes. Aztreonam is resistant to some β-lactamases, but is inactivated by extended-spectrum β-lactamases. Cefotetan and cefoxitin are considered cephamycins and demonstrate a spectrum of activity similar to the second generation cephalosporins. The carbapenems include doripenem, ertapenem, imipenem/cilastatin and meropenem. These agents have a broad spectrum of activity and their chemical structure renders them highly resistant to β-lactamases.

The miscellaneous β-lactam antibiotics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the injectable products are available in a generic formulation, with the exception of doripenem and ertapenem. This class was last reviewed in August 2009.

Table 1. Miscellaneous β-Lactam Antibiotics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Aztreonam	inhalation solution, injection	Azactam®*, Azactam-Iso-Osmotic Dextrose®, Cayston®	aztreonam
Cefotetan	injection	N/A	cefotetan
Cefoxitin	injection	Mefoxin®	cefoxitin
Doripenem	injection	Doribax®	none
Ertapenem	injection	Invanz®	none
Imipenem and cilastatin	injection	Primaxin®*, Primaxin IM®	imipenem and cilastatin
Meropenem	injection	Merrem®*	meropenem

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

The miscellaneous β-lactam antibiotics have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the miscellaneous β-lactam antibiotics that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Miscellaneous β-Lactam Antibiotics[1-10]

Organism	Aztreonam†	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Imipenem/Cilastatin	Meropenem
Gram-Positive Aerobes							
Enterococcus faecalis						✔ §‡	✔
Staphylococcus aureus		✔	✔		✔	✔ §‡	✔
Staphylococcus epidermidis		✔	✔			✔ ‡	
Streptococcus species		✔	✔				
Streptococcus agalactiae		✔	✔		✔	✔ ‡	✔
Streptococcus constellatus				✔			
Streptococcus intermedius				✔			
Streptococcus pneumoniae		✔	✔		✔	✔ §‡	✔
Streptococcus pyogenes		✔	✔		✔	✔ §‡	✔
Streptococcus viridans group						✔ §	✔
Gram-Negative Aerobes							
Acinetobacter species						✔ §‡	
Acinetobacter baumannii				✔			
Acinetobacter calcoaceticus						✔ §	
Citrobacter species	✔					✔ §‡	
Citrobacter freundii	✔						
Enterobacter species	✔					✔ §‡	
Enterobacter cloacae	✔					✔ §	
Escherichia coli	✔	✔	✔	✔	✔	✔ §‡	✔
Gardnerella vaginalis						✔ ‡	
Haemophilus influenzae	✔	✔	✔		✔	✔ §‡	✔
Haemophilus parainfluenzae						✔ ‡	
Klebsiella species	✔	✔	✔		✔	✔ §‡	
Klebsiella oxytoca	✔						
Klebsiella pneumoniae	✔	✔	✔	✔	✔	✔ §	✔
Moraxella catarrhalis					✔		
Morganella morganii		✔	✔			✔ ‡	
Neisseria gonorrhoeae		✔	✔				
Neisseria meningitidis							✔
Proteus species		✔					
Proteus mirabilis	✔	✔	✔	✔	✔		✔
Proteus vulgaris		✔	✔			✔ ‡	
Providencia species			✔				
Providencia rettgeri		✔	✔			✔ ‡	

Organism	Aztreonam†	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Imipenem/Cilastatin	Meropenem
Pseudomonas aeruginosa	✔			✔		✔ §‡	✔
Serratia species	✔					✔ ‡	
Serratia marcescens	✔	✔				✔ ‡	
Gram-Positive Anaerobes							
Clostridium species		✔	✔			✔ ‡	
Clostridium clostridioforme					✔		
Eubacterium species						✔ ‡	
Eubacterium lentum					✔		
Peptococcus species						✔ ‡	
Peptococcus niger		✔	✔				
Peptostreptococcus species		✔	✔		✔	✔ §‡	✔
Peptostreptococcus micros				✔			
Porphyromonas asaccharolyctica					✔		
Prevotella bivia		✔			✔		
Prevotella disiens		✔					
Prevotella melaninogenica		✔					
Propionibacterium species						✔ ‡	
Gram-Negative Anaerobes							
Bacteroides species			✔			✔ §‡	
Bacteroides caccae				✔			
Bacteroides distasonis			✔		✔	✔ §	
Bacteroides fragilis		✔	✔	✔	✔	✔ §‡	✔
Bacteroides intermedius						✔ §	
Bacteroides ovatus			✔		✔		
Bacteroides thetaiotaomicron			✔	✔	✔	✔ §	✔
Bacteroides uniformis				✔	✔		
Bacteroides vulgatus		✔		✔			
Bifidobacterium species						✔ ‡	
Fusobacterium species		✔				✔ §‡	

†Injection formulation
‡Intramuscular formulation
§Intravenous formulation

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous β-lactam antibiotics are summarized in Table 3.

Table 3. Treatment Guidelines Using the Miscellaneous β-Lactam Antibiotics

Clinical Guideline	Recommendation(s)
American Heart Association (AHA): **Infective Endocarditis: Diagnosis, Antimicrobial Therapy, and Management of Complications[20] (2005)**	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus bovis*: o Penicillin-susceptible strains ▪ Penicillin G or ceftriaxone for 4 weeks ▪ Penicillin G or ceftriaxone plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Penicillin-resistant strains: ▪ Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus bovis*: o Penicillin-susceptible strains ▪ Penicillin G or ceftriaxone for 6 weeks with or without gentamicin for 2 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Penicillin-resistant strains: ▪ Penicillin G or ceftriaxone for 6 weeks plus gentamicin for 6 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for 6 weeks with the option of adding gentamicin for 3-5 days ▪ For penicillin-allergic individuals: cefazolin for 6 weeks with the option of adding gentamicin for 3-5 days o Oxacillin-resistant strains ▪ Vancomycin for 6 weeks • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) o Oxacillin-resistant strains ▪ Vancomycin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) • Therapy for native valve or prosthetic valve enterococcal endocarditis o Strains susceptible to penicillin, gentamicin, and vancomycin: ▪ Ampicillin or penicillin G plus gentamicin for 4-6

Clinical Guideline	Recommendation(s)
	weeks ▪ Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Strains susceptible to penicillin, streptomycin, and vancomycin and resistant to gentamicin: ▪ Ampicillin or penicillin G plus streptomycin for 4-6 weeks ▪ Vancomycin plus streptomycin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Strains resistant to penicillin and susceptible to aminoglycosides and vancomycin: ▪ β-lactamase–producing strain: • Ampicillin-sulbactam plus gentamicin for 6 weeks • Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for 6 weeks o Strains resistant to penicillin, aminoglycosides and vancomycin: ▪ *E. faecium*: linezolid or quinupristin-dalfopristin for at least 8 weeks ▪ *E. faecalis*: imipenem/cilastatin plus ampicillin or ceftriaxone plus ampicillin for at least 8 weeks • Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin-sulbactam or ciprofloxacin for 4-6 weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin, gatifloxacin, or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin for 4-6 weeks ▪ Vancomycin plus gentamicin plus ciprofloxacin for 4-6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillins) o Prosthetic valve (early, <1 year): ▪ Vancomycin (for 6 weeks) plus gentamicin (for 2 weeks) plus cefepime (for 6 weeks) plus rifampin (for 6 weeks) o Prosthetic valve (late, ≥1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone (for 6 weeks) plus gentamicin (for 2 weeks) with or without doxycycline (for 6 weeks) ▪ Documented *Bartonella*, culture positive: • Doxycycline (for 6 weeks) plus gentamicin for (2 weeks)
European Federation of	Empirical Therapy

Clinical Guideline	Recommendation(s)

Neurological Societies (EFNS): **Guideline on the Management of Community-acquired Bacterial Meningitis[87] (2008)**	• Ceftriaxone 2 g every 12–24 hours or cefotaxime 2 g every 6–8 hours.
	• Alternative therapy: Meropenem 2 g every 8 hours or chloramphenicol 1 g every 6 hours.
	• If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg.
	• Ampicillin/amoxicillin 2 g every 4 hours if *Listeria* is suspected.
	<u>Pathogen Specific Therapy</u>
	• Penicillin-sensitive pneumococcal meningitis:
	  o Benzyl penicillin 250,000 U/kg/day, ampicillin/amoxicillin 2 g every 4 hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every 6–8 hours
	  o Alternative therapy: meropenem 2 g every 8 hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily
	• Pneumococcus with reduced susceptibility to penicillin or cephalosporins:
	  o Ceftriaxone or cefotaxime plus vancomycin ± rifampicin
	  o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin
	• Meningococcal meningitis:
	  o Benzyl penicillin, ceftriaxone, or cefotaxime
	  o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin
	• *Haemophilus influenzae* type B:
	  o Ceftriaxone or cefotaxime
	  o Alternative therapy: chloramphenicol–ampicillin/amoxicillin
	• Listerial meningitis:
	  o Ampicillin or amoxicillin 2 g every 4 hours ± gentamicin 1–2 mg every 8 hours for the first 7– 10 days
	  o Alternative therapy: trimethoprim–sulfamethoxazole 10–20 mg/kg every 6–12 hours or meropenem
	• *Staphylococcal* species:
	  o Flucloxacillin 2 g every 4 hours or vancomycin if penicillin allergy is suspected.
	  o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis.
	• Gram-negative *Enterobacteriaceae*:
	  o Ceftriaxone, cefotaxime or meropenem
	• Pseudomonal meningitis:
	  o Meropenem ± gentamicin

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Bacterial Meningitis[19] (2004)**	<u>Empiric Therapy</u> • Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative CSF Gram stain result: • Penetrating head trauma: Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem • Postneurosurgery: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem • CSF shunt: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem <u>Specific Therapy</u> • Recommendations for specific antimicrobial therapy in bacterial

Clinical Guideline	Recommendation(s)

	meningitis are based on isolated pathogens and susceptibility.
	• *Streptococcus pneumoniae*
	  o Penicillin MIC 0.1-1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include cefepime or meropenem
	• *Neisseria meningitides*
	  o Penicillin MIC 0.1- 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include chloramphenicol, a fluoroquinolone or meropenem
	• *Listeria monocytogenes*
	  o Standard therapy includes ampicillin or penicillin G; alternative therapies include trimethoprim-sulfamethoxazole or meropenem
	• *Escherichia coli* and other enterobacteriaceae
	  o Standard therapy includes a third-generation cephalosporin; alternative therapies include aztreonam, fluoroquinolone, meropenem, trimethoprim-sulfamethoxazole or ampicillin
	• *Pseudomonas aeruginosa*
	  o Standard therapies include cefepime or ceftazidime; alternative therapies include aztreonam, ciprofloxacin, or meropenem (addition of an aminoglycoside should be considered)
	• *Staphylococcus aureus* methicillin susceptible
	  o Standard therapy includes nafcillin or ofloxacin; alternative therapies include vancomycin or meropenem

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections[11] (2005)**	<u>Animal Bites</u> • Intravenous treatment options o β-lactam/β-lactamase combinations, piperacillin/tazobactam, second-generation cephalosporins, and carbapenems. <u>Human Bites</u> • Clenched-fist injuries often require hospitalization and intravenous antimicrobial therapy with agents such as cefoxitin, ampicillin/sulbactam, ertapenem, or some combination that covers *S. aureus, Haemophilus* species, *E. corrodens,* and β-lactamase–producing anaerobes. <u>Necrotizing Infections</u> • Antimicrobial therapy must be directed at the pathogens and used in appropriate doses until repeated operative procedures are no longer needed, the patient has demonstrated obvious clinical improvement, and fever has been absent for 48–72 h. • The best choice of antibiotics for community-acquired mixed infections is a combination of ampicillin-sulbactam plus clindamycin plus ciprofloxacin. The carbapenems, or a combination of cefotaxime plus metronidazole or clindamycin, are also appropriate. In cases of penicillin allergy, alternatives include clindamycin or metronidazole plus an aminoglycoside or fluoroquinolone. <u>Surgical Site Infections</u> • If there is minimal surrounding evidence of invasive infection (<5 cm of erythema and induration), and if the patient has minimal systemic signs of infection (a temperature of <38.5°C and a pulse rate of <100 beats/min), antibiotics are unnecessary. • For patients with a temperature of >38.5°C or a pulse rate of >100 beats/min, a short course of antibiotics, usually for a duration of 24–48 h, may be indicated. The antibiotic choice is usually empirical but can be supported by findings of Gram stain and results of culture of the

Clinical Guideline	Recommendation(s)
	wound contents. • For intestinal or genital tract surgical site infections, single agents such as cefoxitin, ceftizoxime, ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam, or carbapenems are indicated. In cases where facultative and aerobic activity is desired, fluoroquinolones, third-generation cephalosporins, aztreonam, or aminoglycosides are recommended. When anaerobic activity is desired, appropriate treatment includes clindamycin, metronidazole, chloramphenicol or a penicillin agent plus a β-lactamase inhibitor. • In axillary or perineum surgical site infections, cefoxitin, ampicillin-sulbactam or agents indicated for intestinal and genital sites are appropriate.
Infectious Diseases Society of America (IDSA): **Diagnosis and Treatment of Diabetic Foot Infections**[85] **(2004)**	• Empirical antibiotic regimens should be based on the clinical severity of the infection. • Current clinical data does not allow for the recommendation of any specific antibiotic regimen for diabetic foot infections (DFIs). • Suggested agents are derived from available published clinical trials and expert experience. • Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have US Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid is currently specifically approved for diabetic foot infections. • Suggested empirical antibiotic regimens for mild infections: dicloxacillin, clindamycin, cephalexin, trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, levofloxacin • Suggested empirical antibiotic regimens for moderate infections: trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, levofloxacin, cefoxitin, ceftriaxone, ampicillin/sulbactam, linezolid (with or without aztreonam), daptomycin (with or without aztreonam), ertapenem, cefuroxime (with or without metronidazole), ticarcillin/clavulanate, piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin • Suggested empirical antibiotic regimens for severe infections: piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin, imipenem-cilastatin, vancomycin and ceftazidime (with or without metronidazole)

Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines**[12] **(2010)**	<u>Pelvic Inflammatory Disease</u>
	• Recommended parenteral regimen A:
	  o Cefotetan 2 g IV every 12 hours
	  o Cefoxitin 2 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours
	• Recommended parenteral regimen B:
	  o Clindamycin 900 mg IV every 8 hours plus gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) can be substituted.
	• Alternative parenteral regimens:
	  o Ampicillin/Sulbactam 3 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours
	• Recommended oral regimen:
	  o Ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg orally twice a day for 14 days with or without

Clinical Guideline	Recommendation(s)
	metronidazole 500 mg orally twice a day for 14 days o Cefoxitin 2 g IM in a single dose and probenecid, 1 g orally administered concurrently in a single dose, plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days o Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
Infectious Diseases Society of America (IDSA)/European Society for Microbiology and Infectious Diseases (ESCMID): **International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women[14] (2010)**	Acute Pyelonephritis • Oral ciprofloxacin (500 mg BID) for 7 days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice when resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. A long-acting antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) may replace the initial one time IV ciprofloxacin, and is recommended if the fluoroquinolone resistance is thought to exceed 10%. • Once-daily fluoroquinolones (ciprofloxacin 100 mg extended-release for 7 days, levofloxacin 750 mg for 5 days) is an appropriate choice when resistance to community uropathogens is not known to exceed 10%. If resistance is thought to exceed 10%, an initial intravenous dose of long-acting parenteral antimicrobial (ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral trimethoprim/sulfamethoxazole (160/800 mg BID) for 14 days is an appropriate choice of therapy when the uropathogen is known to be susceptible. If susceptibility is unknown, an initial IV dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral β-lactams are less effective than other available agents for the treatment of pyelonephritis. If an oral β-lactam is used, an initial IV dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • For patients requiring hospitalization, initial treatment with an intravenous antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin with or without an aminoglycoside, or a carbapenem is recommended. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results.
American College of Obstetricians and Gynecologists (ACOG): **Treatment of Urinary Tract Infections in Nonpregnant Women[13] (2008)**	• For uncomplicated acute bacterial cystitis, recommended treatment regimens are as follows: o Trimethoprim–sulfamethoxazole: 1 tablet (160 mg trimethoprim–800 mg sulfamethoxazole) twice daily for 3 days. o Trimethoprim 100 mg twice daily for 3 days. o Ciprofloxacin 250 mg twice daily for 3 days, levofloxacin 250 mg once daily for 3 days, norfloxacin 400 mg twice daily for 3 days, or gatifloxacin 200 mg, once daily for 3 days. o Nitrofurantoin macrocrystals 50 to 100 mg 4 times daily for 7 days, or nitrofurantoin monohydrate 100 mg twice daily for 7 days. o Fosfomycin tromethamine, 3-g dose (Powder) single dose.
American College of Chest Physicians (ACCP): **Chronic Cough Due to Acute Bronchitis, ACCP Evidence-Based Clinical**	• For patients with the putative diagnosis of acute bronchitis, routine treatment with antibiotics is not justified and should not be offered.

Clinical Guideline	Recommendation(s)
Practice Guidelines[18] (2006)	
American College of Chest Physicians (ACCP): **Chronic Cough Due to Chronic Bronchitis, ACCP Evidence-Based Clinical Practice Guidelines[17] (2006)**	• In stable patients with chronic bronchitis, there is no role for long-term prophylactic therapy with antibiotics. • In patients with acute exacerbations of chronic bronchitis, the use of antibiotics is recommended; patients with severe exacerbations and those with more severe airflow obstruction at baseline are the most likely to benefit.

Global Initiative for Chronic Obstructive Lung Disease (GOLD): **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[16] (2010)**	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in COPD.
	• There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful.
	• Based on current available evidence, antibiotics should be given to:
	  o Patients with exacerbations of COPD with the following three cardinal symptoms: dyspnea, sputum volume, and sputum purulence.
	  o Patients with exacerbations of COPD with two of the cardinal symptoms, if the increased purulence of sputum is one of the two symptoms.
	  o Patients with a severe exacerbation of COPD that requires mechanical ventilation (invasive or noninvasive).
	• Antibiotic treatment in exacerbations of COPD:
	  o Group A (mild exacerbation; no risk factors for poor outcome)
	  ▪ Recommended oral treatment: β-lactam (penicillin, ampicillin, amoxicillin), tetracycline, or trimethoprim-sulfamethoxazole
	  ▪ Alternative oral treatment: β-lactam/β-lactamase inhibitor, macrolides, second or third generation cephalosporin, or ketolides
	  o Group B (moderate exacerbation with risk factor(s) for poor outcome)
	  ▪ Recommended oral treatment: β-lactam/β-lactamase inhibitor
	  ▪ Alternative oral treatment: fluoroquinolones (gemifloxacin, levofloxacin, moxifloxacin)
	  ▪ Parenteral treatment: β-lactam/β-lactamase inhibitor, second or third generation cephalosporin, or fluoroquinolones (levofloxacin, moxifloxacin)
	  o Group C (severe exacerbation with risk factors for *P. aeruginosa* infection)
	  ▪ Recommended oral treatment: fluoroquinolones (ciprofloxacin, levofloxacin)
	  ▪ Parenteral treatment: fluoroquinolones (ciprofloxacin, levofloxacin) or β-lactam with *P. aeruginosa* activity

Cystic Fibrosis Foundation (CFF): **Cystic Fibrosis Pulmonary Guidelines[88] (2007)**	<u>Aerosolized Antibiotics</u> • For patients with cystic fibrosis (CF), 6 years of age and older, who have moderate to severe lung disease and with *P. aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin to improve lung function and reduce exacerbations is recommended. • For patients with CF, age 6 years and older who are asymptomatic or with mild lung disease, and with *P. aeruginosa* persistently present in

Clinical Guideline	Recommendation(s)
	cultures of the airways, the chronic use of inhaled tobramycin to reduce exacerbations is recommended. • For patients with CF, age 6 years and older, with *P. aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing other chronically inhaled antibiotics (i.e., colistin, gentamicin, ceftazidime) to improve lung function and reduce exacerbations. Macrolide Antibiotics • For patients with CF, 6 years of age and older, and with *P. aeruginosa* persistently present in cultures of the airways, the chronic use of azithromycin to improve lung function and to reduce exacerbations is recommended. Antistaphylococcal Antibiotics • For patients with CF, the prophylactic use of oral antistaphylococcal antibiotics to improve lung function and to reduce exacerbations is not recommended.

Infectious Diseases Society of America (IDSA): **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age**[89] **(2011)**	Outpatient Treatment
	• Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia (CAP), because viral pathogens are responsible for the great majority of clinical disease.
	• Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate CAP suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*.
	• For patients allergic to amoxicillin, the following agents are considered alternative treatment options:
	  o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil)
	  o Levofloxacin (oral therapy)
	  o Linezolid (oral therapy)
	• Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with CAP caused by atypical pathogens.
	Inpatient Treatment
	• Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with CAP when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *S. pneumoniae*.
	• Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema.
	• Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America.
	• Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *M. pneumoniae* and *C. pneumoniae* are significant considerations.
	• Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or

Clinical Guideline	Recommendation(s)
	imaging characteristics are consistent with infection caused by *S. aureus*.

Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS): **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults**[15] **(2007)**	Empirical Antimicrobial Therapy
	• Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.
	• Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.
	• Outpatient treatment
	  o Previously healthy and no risk factors for drug-resistant *S. pneumoniae* (DRSP) infection:
	  ▪ Macrolide (azithromycin, clarithromycin, or erythromycin)
	  ▪ Doxycycline
	  o Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected); or other risks for DRSP infection:
	  ▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin)
	  ▪ β-lactam plus a macrolide (High-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide.)
	  o In regions with a high rate of infection with high-level macrolide-resistant *S. pneumoniae,* consider the use of alternative agents listed above in recommendation 16 for any patient, including those without comorbidities.
	• Inpatient, non-ICU treatment
	  o Respiratory fluoroquinolone
	  o β-lactam plus a macrolide (Preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients.)
	• Inpatient, ICU treatment
	  o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended.)
	  o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (Piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam).
	  o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.

American College of Chest	• Antibiotic choice and route of administration are central to an

Clinical Guideline	Recommendation(s)
Physicians (ACCP): **Management of Community-Acquired Pneumonia in the Home: An American College of Chest Physicians Clinical Position Statement[90]** **(2005)**	appropriate in-home treatment plan. The oral route is recommended if the patient can tolerate it, and if the availability and activity of the agent are adequate. • Although treatment is facilitated if the etiologic agent is known (pathogen-directed treatment for CAP is provided in the IDSA guidelines), most outpatient treatment is empiric. • The use of a macrolide, doxycycline, or fluoroquinolone agent, as recommended both by the IDSA and the ATS guidelines, may be appropriate empiric outpatient treatment for low-risk patients (i.e., otherwise young healthy individuals). Alternatives to these agents in low-risk patients are amoxicillin/clavulanate and some second-generation cephalosporins (e.g., cefuroxime, cefpodoxime, or cefprozil). • A lack of response to treatment with macrolides and fluoroquinolones has been reported. Some authorities prefer to reserve the use of fluoroquinolones for older patients, patients who are allergic or intolerant to macrolides, patients who have recently received macrolide treatment, patients with comorbidities, patients with documented infections with highly resistant pneumococci, or patients with a lack of response to treatment with another agent. • The IDSA and ATS recommendations generally agree that a patient who is at high risk either because of complicated comorbidities or extensive prior antibiotic use may be a candidate for treatment with either a β-lactam/macrolide combination or a antipneumococcal fluoroquinolone. • Double therapy with either a β-lactam/macrolide combination or a β-lactam/ antipneumococcal fluoroquinolone should be considered in patients who would normally be considered for ICU admission but have chosen to remain in the home.

American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA):
Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia[23]
(2005)
	• Select an initial empiric therapy based on the absence or presence of risk factors for multidrug-resistant (MDR) pathogens. These risk factors include prolonged duration of hospitalization (5 days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy.
	• Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins.
	• In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics.
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for MDR pathogens, early onset, and any disease severity:
	  o Ceftriaxone OR
	  o Levofloxacin, moxifloxacin, ciprofloxacin OR
	  o Ampicillin/sulbactam OR
	  o Ertapenem
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for MDR pathogens and all disease severity – combination antibiotic therapy is recommended as follows:
	  o Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or

Clinical Guideline	Recommendation(s)
	β-lactam/β-lactamase inhibitor (Piperacillin/tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if MRSA risk factors are present or there is a high incidence locally.
Infectious Diseases Society of America (IDSA): **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children[21] (2010)**	Community-Acquired Infection in Adults: Mild to Moderate Severity • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*E. Coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. Community-Acquired Infection in Adults: High Severity • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *E. coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E. coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended. • Use of agents effective against MRSA or yeast is not recommended in the absence of evidence of infection due to such organisms. Community-Acquired Infection in Pediatric Patients: • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with

Clinical Guideline	Recommendation(s)
	metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected MRSA or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. <u>Health Care-Associated Infection:</u> • Therapy should be based on microbiologic results. To achieve empiric coverage, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. <u>Cholecystitis and Cholangitis:</u> • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder.

Infectious Diseases Society of America (IDSA): **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer**[86] **(2010)**	<u>Initial Antibiotic Therapy</u>
	• Oral route:
	  o For low-risk adults only; use ciprofloxacin plus amoxicillin-clavulanate
	• Monotherapy with vancomycin not indicated:
	  o Choose therapy with 1 of the following agents: cefepime or ceftazidime, or imipenem or meropenem
	• Two drugs without vancomycin:
	  o Choose an aminoglycoside plus antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem
	• Vancomycin plus 1 or 2 antibiotics:
	  o Choose cefepime or ceftazidime plus vancomycin, with or without an aminoglycoside; carbapenem plus vancomycin, with or without an aminoglycoside; or antipseudomonal penicillin plus an aminoglycoside and vancomycin
	<u>Modification of Therapy During the First Week of Treatment</u>
	• Patient becomes afebrile in 3–5 days:
	  o Adjust therapy to the most appropriate drug(s). If no etiologic agent is identified and if the patient is at low risk initially, and oral antibiotic treatment was begun with no subsequent complications, continue use of the same drugs.
	  o If the patient was at low risk initially and therapy with intravenous drugs was begun with no subsequent complications, the regimen may be changed after 48 h to oral ciprofloxacin plus amoxicillin-clavulanate for adults or cefixime for children.

Clinical Guideline	Recommendation(s)
	○ If the patient is at high risk initially with no subsequent complications, continue use of the same intravenous drugs. • Persistent fever throughout the first 3–5 days: ○ Reassess therapy on day 3. If there is no clinical worsening, continue use of the same antibiotics; stop vancomycin use if cultures do not yield organisms. ○ If there is progressive disease, change antibiotics. ○ If the patient is febrile after 5 days, consider adding an antifungal drug
Surgical Infection Prevention Guideline Writers Workgroup (SIPGWW): **Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project[22] (2004)**	General Considerations • There is published evidence to support the use of many prophylactic antimicrobial regimens besides those included in this advisory statement or in existing guidelines. • Factors such as cost, half-life, safety, and antimicrobial resistance favor the use of older agents with a relatively narrow spectrum. • The use of newer, broad-spectrum drugs that are front-line therapeutic agents should be avoided in surgical prophylaxis to reduce emergence of bacterial strains that are resistant to these antimicrobials. Gynecologic and Obstetrical Surgery • For abdominal or vaginal hysterectomy, cefotetan is preferred, but reasonable alternatives are cefazolin and cefoxitin. In cases of β-lactam allergy, the workgroup recommends the use of one of the following regimens: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; metronidazole combined with gentamicin or ciprofloxacin; or clindamycin monotherapy. A single 750-mg dose of levofloxacin can be substituted for ciprofloxacin. • For cesarean section, a narrow-spectrum antimicrobial regimen similar to that recommended for hysterectomy provides adequate prophylaxis. Orthopedic Total Joint (Hip and Knee) Arthroplasty • The preferred antimicrobials for prophylaxis in patients undergoing hip or knee arthroplasty are cefazolin and cefuroxime. • Vancomycin or clindamycin may be used in patients with serious allergy or adverse reactions to β-lactams. Cardiothoracic and Vascular Surgery • The recommended antimicrobials for cardiothoracic and vascular operations include cefazolin or cefuroxime. • For patients with serious allergy or adverse reaction to b-lactams, vancomycin is appropriate, and clindamycin may be an acceptable alternative. Colorectal Surgery • Antimicrobial prophylaxis for colorectal operations can consist of an orally administered antimicrobial bowel preparation, a preoperative parenteral antimicrobial, or the combination of both. • Recommended oral prophylaxis consists of neomycin plus erythromycin or neomycin plus metronidazole, initiated no more than 18–24 h before the operation, along with administration of a mechanical bowel preparation. • Cefotetan or cefoxitin are recommended for parenteral prophylaxis, and the combination of parenteral cefazolin and metronidazole is also recommended as an alternative. • For patients with confirmed allergy or adverse reaction to β-lactams, use of one of the following regimens is recommended: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; or metronidazole combined with gentamicin or ciprofloxacin. A single 750-mg dose of levofloxacin can be substituted for ciprofloxacin.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous β-lactam antibiotics are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Miscellaneous β-Lactam Antibiotics[1-10]

Indication	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Imipenem/ Cilastatin	Meropenem
Central Nervous System Infections							
Meningitis							✔
Dermatological Infections							
Abscesses						✔ §	
Burns	✔ ‡						
Cellulitis						✔ §	
Cutaneous infections (adjunctive therapy to surgery)	✔ ‡						
Diabetic foot infections without osteomyelitis					✔		
Infected skin ulcers	✔ ‡					✔ §	
Postoperative wounds	✔ ‡						
Skin and skin-structure infections	✔ ‡	✔	✔		✔	✔ § ‖	✔
Wounds infections						✔ §	
Genitourinary Infections							
Cystitis	✔ ‡						
Endometritis	✔ ‡		✔				
Gynecologic infections	✔ ‡	✔	✔			✔ § ‖	
Pelvic cellulitis	✔ ‡		✔				
Pelvic infections, acute					✔		
Pelvic inflammatory disease			✔				
Postpartum endomyometritis					✔	✔ §	
Postsurgical gynecologic infections					✔		
Pyelonephritis	✔ ‡			✔	✔		
Septic abortion					✔		
Urinary tract infections	✔ ‡	✔	✔	✔	✔	✔ ‖	
Respiratory Infections							
Bronchitis	✔ ‡					✔ §	
Improve respiratory symptoms in cystic fibrosis patients with *P. aeruginosa*	✔ †						

Indication	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Imipenem/ Cilastatin	Meropenem
Lung abscess			✔				
Pneumonia	✔ ‡		✔			✔ §	
Pneumonia (community acquired)					✔		
Respiratory tract infections (lower)	✔ ‡	✔	✔			✔ § ‖	
Miscellaneous Infections							
Abscesses (adjunctive therapy to surgery)	✔ ‡						
Appendicitis						✔ §	✔
Appendicitis with peritonitis						✔ §	
Bone and/or joint infections		✔	✔			✔ ‖	
Endocarditis						✔ ‖	
Infections complicating hollow viscus perforations (adjunctive therapy to surgery)	✔ ‡						
Infections of serous surfaces (adjunctive therapy to surgery)	✔ ‡						
Intra-abdominal infections	✔ ‡	✔	✔	✔	✔	✔ § ‖	✔
Peritonitis	✔ ‡		✔				✔
Polymicrobic infections						✔ ‖	
Perioperative prophylaxis		✔	✔		✔		
Septicemia	✔ ‡		✔			✔ ‖	

†Inhalation solution formulation
‡Injection formulation
§Intramuscular formulation
‖Intravenous formulation

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous β-lactam antibiotics are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Miscellaneous β-Lactam Antibiotics[1-10]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Aztreonam	INH: low IM: 100	56	Liver (7)	INH: Renal (10) IM/IV: Renal (60-70) Feces (12)	INH: 2.1 IM/IV: 1.6-2.9
Cefotetan	N/A	78-91	Not reported	Renal (50-80) Bile (12)	3.0-4.6
Cefoxitin	N/A	41-75	Liver (<2)	Renal (85-90) Bile (<1)	0.8-1.0
Doripenem	N/A	8	Not reported	Renal (70) Feces (<1)	1.0
Ertapenem	IM: 90	85-95	Renal	Renal (>80) Feces (10)	4.0
Imipenem and cilastatin	N/A	I: 20 C: 40	Renal	I: Renal (50-70) C: Renal (70-75)	1.0
Meropenem	N/A	2	Extrarenal (20-25)	Renal (62-83)	1-1.5

INH=inhalation

V. Drug Interactions

Significant drug interactions with the miscellaneous β-lactam antibiotics are listed in Table 6.

Table 6. Significant Drug Interactions with the Miscellaneous β-Lactam Antibiotics[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Cefotetan	1	Anticoagulants	The hypoprothrombinemic effects of anticoagulants may be increased by cefotetan with a possible increased risk of bleeding complications.
Doripenem, ertapenem, imipenem/cilastatin, meropenem	1	Valproic acid	Plasma concentrations and pharmacologic effects of valproic acid may be decreased by carbapenems.
Doripenem, ertapenem, meropenem	2	Probenecid	Plasma concentrations of carbapenems may increase as a result of decreased active tubular secretion with co-administration of probenecid.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous β-lactam antibiotics are listed in Table 7.

Table 7. Adverse Drug Events (%) Reported with the Miscellaneous β-Lactam Antibiotics[1-10]

Adverse Events	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Imipenem/Cilastatin	Meropenem
Cardiovascular							
Arrhythmia	-	-	-	-	<1	-	-
Asystole	-	-	-	-	<1	-	-
Atrial fibrillation	-	-	-	-	<1	-	-
Bradycardia	-	-	-	-	<1	-	<1
Cardiac arrest	-	-	-	-	<1	-	<1
Chest pain	<1†, 8‡	-	-	-	1-2	-	<1
Edema	-	-	-	-	3	-	-
Heart failure	-	-	-	-	<1	-	<1
Heart murmur	-	-	-	-	<1	-	-
Hypertension	-	-	-	-	1-2	-	<1
Hypotension	<1†	-	<1	-	1-2	<1	<1
Myocardial infarction	-	-	-	-	-	-	<1
Palpitations	-	-	-	-	-	<1	-
Shock	-	-	-	-	-	-	1
Syncope	-	-	-	-	<1	-	<1
Tachycardia	-	-	-	-	1-2	≤2	<1
Ventricular tachycardia	-	-	-	-	<1	-	-
Central Nervous System							
Agitation/delirium	-	-	-	-	-	-	<1
Anxiety	-	-	-	-	1	-	<1
Confusion	<1†	-	-	-	-	<1	<1
Delirium	-	-	-	-	<1	-	-
Depression	-	-	-	-	-	-	<1
Dizziness	<1†	-	-	-	2	<1	<1
Encephalopathy	-	-	-	-	-	<1	-
Fatigue	-	-	-	-	1	-	-
Fever	<1†, 13‡	<1	<1	-	2-5	<1	<1
Hallucinations	-	-	-	-	-	<1	<1
Headache	<1†	-	-	4-16	6-7	-	2-8
Insomnia	<1†	-	-	-	3	-	<1
Mental status changes	-	-	-	-	3-5	-	-

Adverse Events	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Imipenem/Cilastatin	Meropenem
Myasthenia gravis exacerbation	-	-	<1	-	-	-	-
Myoclonus	-	-	-	-	<1	<1	-
Nervousness	-	-	-	-	-	-	<1
Paresthesia	<1†	-	-	-	-	<1	<1
Psychic disturbances	-	-	-	-	-	<1	-
Seizures	<1†	-	-	✔	-	≤6	<1
Somnolence	-	-	-	-	-	<1	<1
Tremor	-	-	-	-	-	<1	-
Vertigo	<1†	-	-	-	-	<1	-
Dermatological							
Angioedema	<1†	-	<1	-	-	-	<1
Angioneurotic edema	-	-	-	-	-	<1	-
Dermatitis	-	-	-	1-5	-	-	-
Diaphoresis	<1†	-	-	-	-	-	<1
Erythema	-	-	-	1-5	1-2	-	-
Erythema multiforme	<1†	-	-	1-5	-	<1	<1
Exfoliative dermatitis	<1†	-	<1	-	-	-	-
Flushing	<1†	-	-	-	-	<1	-
Hyperhidrosis	-	-	-	-	-	<1	-
Macular/papular eruptions	-	-	-	1-5	-	-	-
Petechiae	<1†	-	-	-	-	-	-
Pruritus	<1†	<1	<1	≤3	1-2	<1	1
Rash	1-10†, 2‡	<1	<1	1-5	2-3	≤2	2-3
Skin ulcer	-	-	-	-	-	-	<1
Stevens-Johnson syndrome	-	-	-	✔	-	<1	<1
Toxic epidermal necrolysis	<1†	-	<1	✔	-	<1	<1
Urticaria	<1†	<1	<1	1-5	-	<1	<1
Gastrointestinal							
Abdominal cramps	<1†	-	-	-	-	-	-
Abdominal enlargement	-	-	-	-	-	-	<1
Abdominal pain	7‡	-	-	-	4	<1	<1
Abnormal taste	<1†	-	-	-	-	-	-
Acid regurgitation	-	-	-	-	1-2	-	-
Anorexia	-	-	-	-	-	-	<1
Aphthous ulcer	<1†	-	-	-	-	-	-
C. difficile-associated diarrhea	<1†	-	-	-	<1	-	-
Cholelithiasis	-	-	-	-	<1	-	-

Adverse Events	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Imipenem/Cilastatin	Meropenem
Constipation	-	-	-	-	3-4	-	1-7
Diarrhea	1-10†	1	1-10	6-11	9-10	1-4	4-7
Dyspepsia	-	-	-	-	1	-	<1
Dysphagia	-	-	-	-	<1	-	-
Flatulence	-	-	-	-	-	-	<1
Gastritis	-	-	-	-	<1	-	-
Gastroenteritis	-	-	-	-	-	<1	-
Gastrointestinal hemorrhage	-	-	-	-	<1	-	<1
Glossitis	-	-	-	-	-	<1	1
Halitosis	<1†	-	-	-	-	-	-
Hemorrhagic colitis	-	-	-	-	-	<1	-
Ileus	-	-	-	-	<1	-	<1
Intestinal obstruction	-	-	-	-	-	-	<1
Melena	-	-	-	-	-	-	<1
Nausea	1-10†	<1	<1	4-12	6-9	1-2	1-8
Numb tongue	<1†	-	-	-	-	-	-
Oral candidiasis	-	-	-	1	≤1	-	≤2
Pancreatitis	-	-	-	-	<1	-	-
Pseudomembranous colitis	<1†	<1	<1	-	-	<1	-
Tongue papillar hypertrophy	-	-	-	-	-	<1	-
Vomiting	1-10†, 6‡	<1	<1	-	4	≤2	1-8
Genitourinary							
Abnormal urinalysis	-	-	-	-	-	<1	-
Dysuria	-	-	-	-	-	-	<1
Hematuria	-	-	-	-	1-3	-	<1
Interstitial nephritis	-	-	<1	-	-	-	-
Nephrotoxicity	-	<1	<1	-	-	-	-
Oliguria/anuria	-	-	-	-	<1	≤2	-
Pelvic pain	-	-	-	-	-	-	<1
Polyuria	-	-	-	-	-	<1	-
Pyuria	-	-	-	-	2-3	-	-
Renal impairment/failure	-	-	-	≤1	<1	<1	<1
Urinary incontinence	-	-	-	-	-	-	<1
Vaginal candidiasis	-	-	-	-	-	-	<1
Vaginitis	<1†	-	-	-	1-3	-	-
Vulvomycotic infection	-	-	-	1-2	-	-	-
Hematologic							

Adverse Events	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Imipenem/Cilastatin	Meropenem
Agranulocytosis	-	<1	-	-	-	<1	<1
Anemia	<1†	-	-	2-10	-	<1	≤6
Bone marrow depression	-	-	<1	-	-	<1	-
Eosinophilia	<1†	<1	<1	-	1-2	<1	<1
Hematocrit decreased	-	-	-	-	3-5	-	-
Hemoglobin decreased	-	-	-	-	3-5	-	-
Hemolytic anemia	-	<1	<1	-	-	<1	<1
Leukocytosis	-	-	-	-	-	<1	<1
Leukopenia	<1†	<1	<1	✔	1-2	<1	<1
Neutropenia	<1†	-	-	✔	1-2	<1	<1
Pancytopenia	<1†	-	-	-	-	<1	-
PT decreased	-	-	-	-	-	-	<1
PT increased	-	-	-	-	≤1	-	-
PTT decreased	-	-	-	-	-	-	<1
Thrombocythemia	-	-	-	-	-	<1	-
Thrombocytopenia	<1†	<1	-	-	1	<1	<1
Thrombocytosis	-	<1	-	-	4-7	-	<1
Hepatic							
Hepatic failure	-	-	-	-	-	<1	<1
Hepatitis	<1†	-	-	-	-	<1	-
Jaundice	<1†	-	<1	-	<1	<1	<1
Laboratory Test Abnormalities							
Albumin decreased	-	-	-	-	1-2	-	-
Alkaline phosphatase increased	-	-	-	-	4-7	<1	<1
ALT increased	<1†	1	<1	1-2	7-9	<1	<1
AST increased	<1†	1	<1	1-2	7-9	<1	<1
BUN increased	-	<1	<1	-	-	<1	<1
Hematocrit decreased	-	-	-	-	-	<1	<1
Hemoglobin decreased	-	-	-	-	-	<1	<1
Hyperbilirubinemia	-	-	-	-	<1	-	<1
Hyperchloremia	-	-	-	-	-	<1	-
Hyperglycemia	-	-	-	-	1-2	-	-
Hyperkalemia	-	-	-	-	≤1	<1	-
Hypoglycemia	-	-	-	-	-	-	✔
Hypokalemia	-	-	-	-	2	-	<1
Hyponatremia	-	-	-	-	-	<1	-
LDH increased	-	-	-	-	-	<1	<1

Adverse Events	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Imipenem/Cilastatin	Meropenem
Positive Coombs' test	-	-	-	-	-	<1	<1
PT prolonged	-	<1	<1	-	-	<1	-
Serum creatinine increased	-	<1	<1	-	1	<1	<1
Musculoskeletal							
Asthenia	-	-	-	-	-	<1	-
Back pain	-	-	-	-	-	-	<1
Dyskinesia	-	-	-	-	<1	-	-
Leg pain	-	-	-	-	≤1	-	-
Myalgia	<1†	-	-	-	-	-	-
Polyarthralgia	-	-	-	-	-	<1	-
Weakness	<1†	-	-	-	1	-	<1
Respiratory							
Apnea	-	-	-	-	-	-	1
Asthma	-	-	-	-	<1	-	<1
Bronchoconstriction	-	-	-	-	<1	-	-
Bronchospasm	<1†, 3‡	-	-	-	-	-	-
Cough	54‡	-	-	-	1-2	-	<1
Cyanosis	-	-	-	-	-	<1	-
Dyspnea	<1†	-	<1	-	1-3	<1	<1
Hemoptysis	-	-	-	-	<1	-	-
Hypoxemia	-	-	-	-	<1	-	-
Hypoxia	-	-	-	-	-	-	<1
Hyperventilation	-	-	-	-	-	<1	-
Interstitial pneumonia	-	-	-	✔	-	-	-
Nasal congestion	16‡	-	-	-	-	-	-
Pharyngeal pain	12‡	-	-	-	-	<1	-
Pharyngitis	-	-	-	-	1	-	✔
Pleural effusion	-	-	-	-	<1	-	<1
Pneumonia	-	-	-	-	-	-	✔
Pulmonary edema	-	-	-	-	-	-	<1
Pulmonary embolus	-	-	-	-	-	-	<1
Rales/rhonchi	-	-	-	-	1	-	-
Respiratory disorder	-	-	-	-	-	-	<1
Respiratory distress	-	-	-	-	≤1	-	-
Sneezing	<1†	-	-	-	-	-	-
Wheezing	<1†, 16‡	-	-	-	-	-	-
Other							

Adverse Events	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Imipenem/Cilastatin	Meropenem
Anaphylactoid reactions	-	-	-	-	<1	-	-
Anaphylaxis	<1†	<1	<1	✔	<1	<1	-
Bleeding	-	<1	-	-	-	-	-
Breast tenderness	<1†	-	-	-	-	-	-
Candidiasis	-	-	-	-	-	<1	-
Chills	-	-	-	-	-	-	<1
Diplopia	<1†	-	-	-	-	-	-
DRESS syndrome	-	-	-	-	<1	-	-
Drug fever	-	-	-	-	-	<1	-
Epistaxis	-	-	-	-	-	-	<1
Extravasation	-	-	-	-	1-2	-	-
Facial edema	<1‡	-	-	-	<1	-	-
Gout	-	-	-	-	<1	-	-
Hearing loss	-	-	-	-	-	<1	-
Hemoperitoneum	-	-	-	-	-	-	<1
Hypersensitivity	<1‡	1	-	-	-	<1	-
Hypervolemia	-	-	-	-	-	-	<1
Inflammation at injection site	-	-	-	-	-	-	2
Infused vein complication	-	-	-	-	5-7	-	-
Injection site edema	-	-	-	-	-	-	<1
Injection site pain	1-10†	-	-	-	-	1	<1
Injection site reaction	-	-	-	-	-	-	1
Pain	-	-	-	-	-	-	≤5
Peripheral edema	-	-	-	-	-	-	<1
Purpura	<1†	-	-	-	-	-	-
Septic shock	-	-	-	-	<1	-	-
Septicemia	-	-	-	-	<1	-	2
Subdural hemorrhage	-	-	-	-	<1	-	-
Thoracic spine pain	-	-	-	-	-	<1	-
Throat tightness	<1‡	-	-	-	-	-	-
Thrombophlebitis/phlebitis	1-10†	<1	<1	4-8	2	3	1
Tinnitus	<1†	-	-	-	-	<1	-

✔ Percent not specified
- Event not reported
‡Inhalation formulation
†Injection formulation

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous β-lactam antibiotics are listed in Table 8.

Table 8. Usual Dosing Regimens for the Miscellaneous β-Lactam Antibiotics[1-10]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Aztreonam	Cystic Fibrosis: Inhalation: 75 mg inhaled 3 times daily for 28 days followed by 28 days off of therapy Moderately Severe Systemic Infections: Injection: 1 to 2 g IM/IV every 8 or 12 hours Severe Systemic or Life-Threatening Infections: 2 g IM/IV every 6 or 8 hours Urinary Tract Infections: Injection: 500 mg to 1 g IM/IV every 8 or 12 hours	Cystic Fibrosis: ≥7 years of age: Inhalation: 75 mg inhaled 3 times daily for 28 days followed by 28 days off of therapy Mild to Moderate Infections: 9 months to 16 years of age: Injection: 30 mg/kg IV every 8 hours Moderate to Severe Infections: 9 months to 16 years of age: Injection: 30 mg/kg IV every 6 or 8 hours	Inhalation solution: 75 mg/ml Injection: 1 g 1 g/50 ml 2 g 2 g/50 ml
Cefotetan	Life-Threatening Infections: 3 g IV every 12 hours Prophylaxis of Postoperative Infections: 1 to 2 g IV administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped. Severe Infections: 2 g IV every 12 hours Skin and Skin-Structure Infections: Mild to moderate infections: 2 g IV every 24 hours or 1 g IV every 12 hours Severe infections: 2 g IV every 12 hours Unspecified Infections: 1 to 2 g IV every 12 hours Urinary Tract Infections: 500 mg IV every 12 hours, 1 or 2 g IV every 24 hours, or 1 or 2 g IV every 12 hours	Safety and efficacy in children have not been established.	Injection: 1 g 1 g/50 ml 2 g 2 g/50 ml 10 g
Cefoxitin	Infections Needing Antibiotics in Higher Doses: 2 g IV every 4 hours or 3 g IV	Prophylaxis of Infections (Uncontaminated GI Surgery, Vaginal Hysterectomy,	Injection: 1 g 1 g/50 ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	every 6 hours Moderately Severe or Severe Infections: 1 g IV every 4 hours or 2 g IV every 6 to 8 hours Prophylaxis of Infections (Uncontaminated GI Surgery, Vaginal Hysterectomy, Abdominal Hysterectomy, or Cesarean Section): 2 g IV administered 30 to 60 minutes prior to surgery, followed by 2 g IV every 6 hours after the first dose for no more than 24 hours. For patients undergoing cesarean section, either a single 2 g dose administered IV as soon as the umbilical cord is clamped or a 3-dose regimen consisting of 2 g given IV as soon as the umbilical cord is clamped, followed by 2 g IV 4 and 8 hours after the initial dose. Uncomplicated Infections (Pneumonia, Urinary Tract Infection, Cutaneous Infection): 1 g IV every 6 to 8 hours	Abdominal Hysterectomy): ≥3 months of age: 30-40 mg/kg administered 30 to 60 minutes prior to surgery, followed by 30-40 mg/kg every 6 hours after the first dose for no more than 24 hours Unspecified Infections: ≥3 months of age: 80 to 160 mg/kg of body weight per day divided into 4 to 6 equal doses	2 g 2 g/50 ml 10 g
Doripenem	Complicated Intra-Abdominal Infections: 500 mg IV every 8 hours Unspecified Infections: 500 mg IV every 8 hours Urinary Tract Infections (Complicated): 500 mg IV every 8 hours	Safety and efficacy in children have not been established.	Injection: 250 mg 500 mg
Ertapenem	Acute Pelvic Infections (Postpartum Endomyometritis, Septic Abortion, Postsurgical Gynecologic Infections): 1 g IM/IV once daily Community-Acquired Pneumonia: 1 g IM/IV once daily Intra-Abdominal Infections (Complicated): 1 g IM/IV once daily Prophylaxis of Surgical Site	Acute Pelvic Infections (Postpartum Endomyometritis, Septic Abortion, Postsurgical Gynecologic Infections): 3 months to 12 years of age: 15 mg/kg IV/IM twice daily ≥13 years of age: 1 g IM/IV once daily Community-Acquired Pneumonia: 3 months to 12 years of age: 15 mg/kg IV/IM twice daily	Injection: 1 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Infections (Colorectal Surgery): Single 1 g dose IV administered 1 hour prior to surgical incision Skin and Skin-Structure Infections (Complicated): 1 g IM/IV once daily Urinary Tract Infections (Complicated): 1 g IM/IV once daily	≥13 years of age: 1 g IM/IV once daily Intra-Abdominal Infections (Complicated): 3 months to 12 years of age: 15 mg/kg IV/IM twice daily ≥13 years of age: 1 g IM/IV once daily Skin and Skin-Structure Infections (Complicated): 3 months to 12 years of age: 15 mg/kg IV/IM twice daily ≥13 years of age: 1 g IM/IV once daily Urinary Tract Infections (Complicated): 3 months to 12 years of age: 15 mg/kg IV/IM twice daily ≥13 years of age: 1 g IM/IV once daily	
Imipenem and cilastatin	Gynecologic Infections (Mild to Moderate): Intramuscular: 500 to 750 mg IM every 12 hours Intra-Abdominal Infections (Mild to Moderate): Intramuscular: 750 mg IM every 12 hours Lower Respiratory Tract Infections (Mild to Moderate): Intramuscular: 500 to 750 mg IM every 12 hours Mild Infections: Fully susceptible organisms: Intravenous: 250 mg IV every 6 hours or 500 mg IV every 6 hours Moderately susceptible organisms: Intravenous: 500 mg IV every 6 hours Moderate Infections: Fully susceptible organisms: Intravenous: 500 mg IV every 8 hours	Gynecologic Infections (Mild to Moderate): ≥12 years of age: Intramuscular: 500 to 750 mg IM every 12 hours Intra-Abdominal Infections (Mild to Moderate): ≥12 years of age: Intramuscular: 750 mg IM every 12 hours Lower Respiratory Tract Infections (Mild to Moderate): ≥12 years of age: Intramuscular: 500 to 750 mg IM every 12 hours Non-CNS Infections: <1 week of age: Intravenous: 25 mg/kg IV every 12 hours 1 to 4 weeks of age: Intravenous: 25 mg/kg IV every 8 hours 4 weeks to 3 months of age: Intravenous: 25 mg/kg IV every 6 hours	Injection: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Moderately susceptible organisms: Intravenous: 500 mg IV every 6 hours or 1 g IV every 8 hours Severe or Life-Threatening Infections: Fully susceptible organisms: Intravenous: 500 mg IV every 6 hours Moderately susceptible organisms: Intravenous: 1 g IV every 8 hours or 1 g IV every 6 hours Skin and Skin-Structure Infections (Mild to Moderate): Intramuscular: 500 to 750 mg IM every 12 hours Urinary Tract Infections: Complicated: Intravenous: 500 mg IV every 6 hours Uncomplicated: Intravenous: 250 mg IV every 6 hours	≥3 months of age: Intravenous: 15 to 25 mg/kg/dose IV every 6 hours Skin and Skin-Structure Infections (Mild to Moderate): ≥12 years of age: Intramuscular: 500 to 750 mg IM every 12 hours	
Meropenem	Intra-Abdominal Infections: 1 g IV every 8 hours Skin and Skin-Structure Infections: 500 mg IV every 8 hours	Intra-Abdominal Infections: ≥3 months of age: ≤50 kg: 20 mg/kg IV every 8 hours >50 kg: 1 g IV every 8 hours Meningitis: ≥3 months of age: ≤50 kg: 40 mg/kg IV every 8 hours >50 kg: 2 g IV every 8 hours Skin and Skin-Structure Infections (Complicated): ≥3 months of age: ≤50 kg: 10 mg/kg IV every 8 hours >50 kg: 500 mg IV every 8 hours	Injection: 500 mg 1 g

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous β-lactam antibiotics are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Miscellaneous β-Lactam Antibiotics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Corey et al.[67] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	RCT, MC, DB, AC Patients ≥18 years of age with complicated skin and skin structure infections (cSSSIs) who required ≥5 days of parenteral antibacterial therapy	N=702 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (8–15 days after administration of the last dose of study medication) in the clinically evaluable (CE) and modified intent-to-treat (MITT) populations Secondary: Microbiological success rate, safety	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the CE (91.1% vs 93.3%; 95% CI, -6.6 to 2.1) and MITT (86.6% vs 85.6%; 95% CI, -4.2 to 6.2) populations, respectively. Secondary: The clinical cure rate for MRSA cSSSIs was 95.1% for ceftaroline and 95.2% for vancomycin plus aztreonam. Similar cure rates were found in patients with MSSA (91.3% and 94.6%), as well as in the patients from whom Gram-negative pathogens were isolated. The microbiological success rate was similar for ceftaroline and vancomycin overall, and for MRSA. Among the ME patients, the baseline pathogen(s) was eradicated or presumed eradicated at similar rates in both the ME and mMITT populations (91.8% and 86.3% for ceftaroline; 92.5% and 83.7% for vancomycin plus aztreonam; 95% CI, -5.7 to 4.4 and 95% CI, -3.4 to 8.9, respectively). The incidence of AEs was similar in both study groups. The majority of AEs were mild in severity and similar in type among study groups. Diarrhea occurred in 3.4% vs 3.2% of patients in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively.
Wilcox et al.[68] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days	RCT, MC, DB, AC Patients ≥18 years of age with complicated skin and skin structure infections (cSSSIs)	N=694 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (8–15 days after administration of the last dose of	Primary: Cure rates at TOC were comparable in both treatment groups across all study populations. In the CE population, cure rates were 92.2% and 92.1% for ceftaroline and vancomycin plus aztreonam, respectively (95% CI, -4.4 to 4.5). In the MITT population, clinical cure rates for ceftaroline and vancomycin plus aztreonam were similar (85.1% vs 85.5%, respectively; 95% CI, -5.8 to 5.0).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ceftaroline 600 mg every 12 hours for 5 to 14 days	who required ≥5 days of parenteral antibacterial therapy		study medication) in the clinically evaluable (CE) and modified intent-to-treat (MITT) populations Secondary: Microbiological success rate, safety	Secondary: In patients with MRSA isolated at baseline, cure rates were 91.4% and 93.3% for ceftaroline and vancomycin plus aztreonam, respectively. Similar cure rates were found in patients with MSSA (94.4% in both groups) as well as in the patients from whom a Gram-negative pathogen was isolated. Baseline pathogens were eradicated or presumed eradicated at similar rates in both the ME and mMITT populations among Gram-positive and a limited number of Gram-negative pathogens (92.9% and 86.6% for ceftaroline; 95.0% and 88.4% for vancomycin plus aztreonam; 95% CI, -6.9 to 2.5 and 95% CI, -7.5 to 3.9, respectively). There were no microbiological reinfections or recurrences at the LFU visit in either treatment group. The incidence of AEs was similar in both study groups. The majority of AEs were mild in severity and similar in type among study groups. Diarrhea occurred in 6.5% vs 4.4% in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively. AEs considered related to the study drug and occurring in ≥3% of patients were diarrhea and pruritus.
Corey et al.[70] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	Pooled analysis (2 trials) Patients ≥18 years of age with complicated skin and skin structure infections (cSSSIs) who required ≥5 days of parenteral antibacterial therapy	N=1,378 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (8–15 days after administration of the last dose of study medication) in the clinically evaluable (CE) and modified intent-to-treat (MITT) populations Secondary:	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the CE (91.6% vs 92.7%) and MITT (85.9% vs 85.5%) populations, respectively. Secondary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in patients infected with MRSA (93.4% vs 94.3%). The efficacy of ceftaroline and vancomycin plus aztreonam against polymicrobial and monomicrobial infections was similar. Clinical relapse at the late follow-up visit was noted in 1.1% of patients in the ceftaroline group compared with 0.9% of patients in the vancomycin plus aztreonam group (CE).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Microbiological success rate, safety	Favorable microbiological response (ME) was observed in 92.3% of patients in the ceftaroline group compared to 93.7% of patients in the vancomycin plus aztreonam group (95% CI, -4.8% to 2.0%). Incidences of treatment-emergent AEs were similar among the treatment groups. Diarrhea occurred in 4.9% of patients in the ceftaroline group and in 3.8% of patients in the vancomycin plus aztreonam group (MITT population). AEs considered to be related to study drug in ≥3% of patients were pruritus, nausea, and diarrhea.
Chuang et al.[72] (2011) Aztreonam 2 g IV every 12 hours plus vancomycin 1 g IV vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours (TGC)	DB, RCT, MC Hospitalized patients ≥18 years of age with complicated skin and skin structure infections (cSSSIs)	N=127 5 to 14 days	Primary: Clinical response in clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) populations Secondary: Clinical response (cure or failure) by baseline isolate and type of infection	Primary: In India, the clinical response rates in the CE and c-mITT populations were higher in the TGC group than in the vancomycin-aztreonam group. CE rates were 83.3% in patients treated with TGC and 75.8% in patients treated with vancomycin-aztreonam. The c-mITT cure rates for TGC vs vancomycin-aztreonam were 78.6% vs 66.7%, respectively. Small sample size prevented non-inferiority analysis. In Taiwan, the clinical response rates in the CE populations were lower in the TGC group than in the vancomycin-aztreonam group. CE rates were 78.6% in patients treated with TGC and 90.0% in patients treated with vancomycin-aztreonam. The c-mITT cure rates for TGC vs vancomycin-aztreonam were 73.3% and 75%, respectively. Small sample size prevented any meaningful statistical analysis. Secondary: In India, the number of isolates was small and no definitive inferences are possible. However, TGC demonstrated antimicrobial efficacy against isolates commonly linked to cSSSIs, including *E. Faecalis, E. Coli, S. aureus and S. agalactiae*. No MRSA isolates were noted among Indian patients. In Taiwan, few isolates were available. They included one patient with MRSA, which responded to TGC.
Gesser et al.[38] (2004)	RCT, PRO, DB, MC	N=146 10-21 days	Primary: Clinical response, adverse events	Primary: For patients receiving OPAT, 83.3% in the ertapenem group and 82.0% in the piperacillin-tazobactam group had a clinical response to therapy and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ertapenem 1 g IV daily vs piperacillin-tazobactam 13.5 grams IV divided every 6 hours Study medications were given as outpatient parenteral antimicrobial therapy (OPAT) or as inpatient therapy	Patients 18 years of age and older with skin and skin structure infections requiring parenteral therapy	post-therapy		were considered cured (P=0.78). The only significant difference in adverse event between the two treatment groups was that 10.5% of patients in the piperacillin-tazobactam group experienced moderate-severe tenderness compared to 0% in the ertapenem group; P=0.006).
Lipsky et al.[39] (2005) Ertapenem 1 g IV daily vs piperacillin-tazobactam 3.375 g every 6 hours Investigators switched patients to oral therapy if appropriate after 5 days of IV therapy.	RCT, DB, MC Adult patients with type 2 diabetes mellitus with a foot infection not extending above the knees	N=445 10 days after completion of antibiotic therapy	Primary: Proportion of patients with a favorable clinical response at the discontinuation of IV therapy (DCIV) Secondary: Proportion of patients with a favorable clinical response at follow-up assessment	Primary: At the DCIV visit, 94% of patients in the ertapenem group and 92% in the piperacillin-tazobactam group had a favorable clinical response. Secondary: At the follow-up assessment visit, 87% of patients in the ertapenem group and 83% in the piperacillin-tazobactam group had a favorable clinical response.
Saltoglu et al.[81] (2010)	RCT, OL, SC Patients ≥18 years	N=64 2 months	Primary: Clinical response	Primary: A successful clinical response was seen in 46.7% of patients in the Pip-Tazo group and in 28.1% of patients in the IMP group (RR, 1.6; (95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Imipenem-cilastatin 0.5 g IV every 6 hours for 14 to 28 days (IMP) vs piperacillin-tazobactam 4.5 g IV every 8 hours for 14 to 28 days (Pip-Tazo)	of age with a diagnosis of moderate to severe diabetic lower extremity foot infection	post-treatment	Secondary: Relapse rate after 2 months	0.84–3.25; P=0.130). Secondary: During 2 months follow-up, two patients in the IMP group and none in the PIP-Tazo group relapsed (RR, 2; 95% CI, 0.94–4.24; P=0.058). Sixty-four percent of patients had amputations. There was no significant difference in amputation rates between the Pip-Tazo and IMP groups (60% vs 68.8%; P=0.739).
Nichols et al.[40] (1995) Meropenem 500 mg IV every 8 hours vs imipenem-cilastatin 500 mg IV every 6 hours	RCT, MC, OL, PRO Hospitalized patients, 18 years of age or older, who required parenteral antibiotics for the treatment of skin or soft tissue infections	N=377 6-7 days	Primary: Clinical response (a response of cured or improved were considered satisfactory) Secondary: Bacteriologic Response	Primary: Satisfactory clinical responses were achieved in 98% of meropenem treated patients and in 95% of imipenem-cilastatin treated patients, a difference that was not significant (95% CI: -2.29 to 6.93). Secondary: Satisfactory bacteriologic response rates were 94% with meropenem and 91% with imipenem-cilastatin, a difference that was not significant (95% CI: -2.73 to 10.39).
Fabian et al.[49] (2005) Meropenem 500 mg IV every 8 hours vs imipenem-cilastatin 500 mg IV every 8 hours	RCT, MC, DB Hospitalized patients with complicated skin and skin-structure infections	N=1,076 14 days	Primary: Clinical response at the post-treatment followup visit in the clinically evaluable (CE) and modified intent-to-treat (MITT) populations Secondary: Clinical response	Primary: The proportion of patients assessed as cured in the CE population at the post-treatment follow-up evaluation was 86.2% for the meropenem and 82.9% for the imipenem-cilastatin treatment groups (95% CI, -2.8 to 9.3). In the MITT population, the clinical cure rates at the follow-up assessment were 73.1% (meropenem) and 74.9% (imipenem-cilastatin; 95% CI, -8.4 to 4.7). Secondary: The clinical response rates at the end of treatment were 93.5% vs 92.3% (CE), 91.0% vs 91.1% (MITT), and 81.0% vs 83.5% (ITT) for meropenem

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			at the post-treatment follow-up visit in the ITT population and at the end-of-treatment visit in the CE, MITT, and ITT populations	and imipenem-cilastatin, respectively. The 95% CI for the difference between treatment groups in all three analysis demonstrated non-inferiority of meropenem to imipenem-cilastatin.
Genitourinary Infections				
Friman et al.[42] (1989) Aztreonam 1 g IV every 8 hours vs cefuroxime 1.5 g IV every 8 hours	RCT Patients 18-99 years of age with symptoms of an upper urinary tract infection	N=171 1 month	Primary: Clinical response rates, bacteriologic response rates	Primary: Clinical response rates were 89% in the aztreonam group and 87% in the cefuroxime group. Bacteriologic response rates at one week post-therapy were 70% in the aztreonam group and 73% in the cefuroxime group, while rates at 1 month were 43% and 40% respectively.
McGregor et al.[66] (1994) Cefoxitin 2 g every 6 hours plus doxycycline 100 mg every 12 hours vs ampicillin-sulbactam 2 g IV every 6 hours vs clindamycin 900 mg IV every 8	RCT, MC, PG Patients diagnosed with pelvic inflammatory disease or endometritis	N=491 Duration varied	Primary: Clinical response	Primary: For pelvic inflammatory disease, the clinical response rate was 85.5% in the ampicillin-sulbactam group and 89.6% in the cefoxitin and doxycycline group (P=0.76). For endometritis, the clinical response rate 88.7% in the ampicillin-sulbactam group and 90.8% in the clindamycin and gentamicin group (P=0.7). There was no significant difference in adverse events between the groups (P=0.12).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours plus gentamicin 1.5 mg/kg IV every 8 hours				
MacGregor et al.[24] (1992) Cefoxitin 2 g IV every 6 hours vs cefotetan 2 g IV every 12 hours	RCT, DB Patients with post-cesarean section endometritis	N=140 Duration varied	Primary: Clinical response, duration of therapy, length of hospital stay	Primary: Cure rates were 83% in the cefotetan group compared to 79% in the cefoxitin group (P=0.56). The duration of therapy and length of hospital stay were similar in both groups.
Naber et al.[80] (2009) Doripenem 500 mg IV every 8 hours vs levofloxacin 250 mg IV once daily Patients in both treatment arms were eligible to switch to oral levofloxacin after 3 days of IV therapy to complete a 10-day treatment course if they demonstrated significant clinical and microbiological	RCT, MC, DB Patients ≥18 years of age with complicated lower urinary tract infections (cUTI) or pyelonephritis who required initial treatment with a parenterally administered antibacterial agent	N=753 Up to 14 days	Primary: Microbiological cure rate in the ME and mMITT population Secondary: Clinical cure rate at the TOC visit for the CE population and the microbiological cure rate for the ME patients infected with *E. coli*	Primary: The ME population achieved microbiological cure rates of 82.1% and 83.4% with doripenem and levofloxacin, respectively. Patients in the mMITT population achieved microbiological cure rates of 79.2% and 78.2%, respectively. Doripenem was not therapeutically inferior to levofloxacin for the treatment of cUTI or pyelonephritis. In the ME population, the microbiological cure rates at the EOT IV were 100% for the doripenem-treated patients and 88% for the levofloxacin-treated patients (P<0.001). The non-inferior response demonstrated for the doripenem-treated patients at the TOC visit could be attributed to the IV portion of the therapeutic regimen, independently of a switch to oral levofloxacin. Secondary: In the CE population, the clinical cure rates at EOT IV were 98.3% and 93.2% in the doripenem and levofloxacin arms, respectively. At the TOC visit, the clinical cure rates were 95.1% and 90.2%, respectively (95% CI, 0.2% to 9.6%). Clinical cure rates at the LFU visit of 90.8% for the doripenem-treated patients and 95.2% for the levofloxacin-treated patients who were CE were sustained.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
improvements.				For the patients who received the IV study drug only, the clinical cure rates at the TOC visit were 78.1% with doripenem and 52.3% with levofloxacin. The microbiological cure rates for *E. coli* infections of ME patients at the TOC visit were 84.4% for the doripenem arm and 87.2% for the levofloxacin arm (P=0.83).
Redman et al.[82] (2010) Study 1 Doripenem 500 mg IV every 8 hours vs levofloxacin 250 mg IV once daily Study 2 Doripenem 500 mg IV every 8 hours After a minimum of 3 days of IV therapy, investigators could switch patients from IV therapy to oral levofloxacin 250 mg daily.	RCT, DB Patients ≥18 years of age with complicated urinary tract infections (cUTI) and pyelonephritis	N=1,179 42 days after the last dose	Primary: Microbiological response at the test-of-cure (TOC) visit (5-11 days after the last dose); clinical cure rates	Primary: Microbiological eradication rates in the microbiologically evaluable patient population at the TOC visit were 82.1% with doripenem and 83.4% with levofloxacin in study 1, and 83.6% with doripenem in study 2. The combined analysis demonstrated that doripenem was non-inferior to levofloxacin. Microbiological eradication rates in the mMITT population at the TOC visit were 79.2% with doripenem and 78.2% with levofloxacin in study 1, and 82.5% with doripenem in study 2.The combined analysis in the mMITT population demonstrated that doripenem was non-inferior to levofloxacin. The pooled microbiological eradication rates in the microbiologically evaluable populations at the TOC and EOT visits from both studies were 99.8% with doripenem and 88.4% with levofloxacin (95% CI, 7.2% to 15.6%). These results suggest that the eradication preceded a switch from IV to oral levofloxacin therapy. Clinical cure rates for the combined clinically evaluable population at the TOC visit were 95.1% with doripenem and 90.2% with levofloxacin in study 1, and 93.0% with doripenem in study 2. The pooled clinical cure rates in the clinically evaluable populations at the TOC and EOT visits showed that clinical improvement preceded a switch to oral levofloxacin; 98.9% with doripenem and 93.2% with levofloxacin in study 1, and 99.6% with doripenem in study 2.
Wells et al.[43] (2004)	RCT, MC	N=480	Primary: Microbiological	Primary: Microbiological response at the TOC visit was 89.4% in the ertapenem

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ertapenem 1 g IV daily vs ceftriaxone 1 g IV daily If appropriate patients could switch to oral therapy after 3 or more days of IV therapy.	Patients 18 years of age and older with complicated urinary tract infections associated with obstruction, foreign body, or urological abnormality interfering with normal voiding	14-18 days	response at the test-of-cure visit (TOC) 5-9 days post-therapy Secondary: Microbiological response at the end of IV therapy, combined microbiological and clinical response at the end of IV therapy, cure rates at TOC visit, microbiological recurrence at the late follow-up visit (LFU) 4-6 weeks post-therapy	group and 91.1% in the ceftriaxone group. There was no significant difference between groups. Secondary: At completion of IV therapy, 98.8% of patients in the ertapenem group and 96.3% in the ceftriaxone group had a favorable microbiological response. At completion of IV therapy, 97.1% of patients in the ertapenem group and 94.8% in the ceftriaxone group had favorable microbiological responses and favorable clinical responses. Cure rates at the TOC visit were 70.7% in the ertapenem group and 70.7% in the ceftriaxone group. Bacterial recurrence rates at the LFU visit were 8.9% in the ertapenem group and 7.6% in the ceftriaxone group.
Cox et al.[44] (1995) Imipenem-cilastatin 500 mg IV QID vs meropenem 500 mg IV TID	MC, OL, PG, PRO, RCT Hospitalized patients ≥18 years of age, with complicated urinary tract infection (UTI) requiring IV antibiotic treatment	N=235 21 days after final dose	Primary: Clinical response (complete resolution or improvement in signs and symptoms of infection), bacteriological response rate (negative urine culture), superinfection, relapse, reinfection	Primary: There was no significant difference in clinical response between the groups (99% for each group) at the end of treatment. At follow-up 83% of the imipenem-cilastatin group and 87% of the meropenem group, reported a satisfactory clinical response. A satisfactory bacterial response was reported in 81% of the patients receiving imipenem-cilastatin and 90% of patients receiving meropenem (95% CI: -1.58 to 19.55; P=0.075). Response at follow-up was observed in 70% in those treated with imipenem-cilastatin and 79% in meropenem recipients. There were few incidences of superinfection or relapse. The same number of patients in each group experienced reinfection. Adverse events were reported in 52% of imipenem-cilastatin recipients and 32% of meropenem patients. There were three patients from the imipenem-cilastatin group and no patients from the meropenem group who withdrew from the study secondary to adverse events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ryo et al.[45] (2005) Imipenem-cilastatin 500 mg IV BID for 3 days plus betamethasone 12 mg SC vs penicillin or a cephalosporin or no antibiotic treatment	RETRO Pregnant women admitted to hospital with preterm premature rupture of membranes (PPROM) at 24 weeks and 0 days to 31 weeks and 6 days gestation	N=140 1 year	Primary: Time from PPROM to delivery, prognosis of infants (death within 1 year, alive with or without handicap) Secondary: Sensitivity of imipenem-cilastatin to cultured bacteria obtained at admission compared to ampicillin	Primary: The mean time from PPROM to delivery was 11.0 days in the imipenem-cilastatin group and 6.0 days in the control group (P=0.016). Also 53% of women treated with imipenem-cilastatin were able to continue pregnancy for greater than one week after PPROM as opposed to 25% in the control group (P=0.0048). There were no infant deaths in the imipenem-cilastatin group but 12.5% of the infants died in the control group (P=0.002). There was no difference in the incidence of infants with handicaps between each group (P=0.3277). Secondary: All cultured bacteria specimens in 94% of the women in the study group were sensitive to imipenem-cilastatin while all specimens found in 25% of those in the control group were sensitive to ampicillin (P<0.0001).
Respiratory Tract Infections				
McCoy et al.[84] (2008) AIR-CF2 Aztreonam inhalation solution 75 mg BID or TID for 28 days (AZLI) vs placebo	RCT, DB, PC, MC Patients ≥6 years of age with cystic fibrosis with FEV_1 >25% and <75% who were on maintenance therapy for *Pseudomonas aeruginosa* (PA) and who had completed a 28-day course of tobramycin inhalation solution	N=211 84 days	Primary: Time to need for additional inhaled or intravenous antipseudomonal antibiotics to treat symptoms indicative of pulmonary exacerbation Secondary: Changes in clinical symptoms, pulmonary function, PA density, time to hospitalization,	Primary: The median time to need for additional inhaled or intravenous antipseudomonal antibiotics to treat symptoms indicative of pulmonary exacerbation was 21 days longer for the AZLI-pooled group than for the placebo group (92 vs. 71 days; P=0.007). The median time to antibiotic need was also longer in the AZLI-BID (>92 days; P=0.002) and AZLI-TID (87 days; P=0.182) groups, compared with placebo (71 days). Secondary: Adjusted mean CFQ-R respiratory scores increased 5.01 points in the AZLI-pooled group compared with placebo (Day 28; 95% CI, 0.81 to 9.21; P=0.020). Significant improvements were observed for both AZLI-BID and AZLI-TID groups compared with placebo and the responses of the AZLI-BID and AZLI-TID groups were comparable. Adjusted mean FEV_1 improved 6.3% in the AZLI-pooled group compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			hospitalizations, and weight	with placebo (Day 28; 95% CI, 2.5–10.1; P=0.001). Significant improvements were observed for both AZLI-BID and AZLI-TID groups compared with placebo. Responses of the AZLI-BID and AZLI-TID groups were comparable. FEV_1 decreased during the follow-up period for all groups. Adjusted mean relative FEV_1% predicted improved in the AZLI-pooled group compared with placebo (Day 28; adjusted means; AZLI-pooled, 4.1%; placebo, 22.5%; 95% CI, 2.8–10.4; P<0.001). Adjusted mean PA sputum density decreased 0.66 log_{10} PA cfu/g sputum in the AZLI-pooled group compared with the placebo group (Day 28: 95% CI. 21.13 to 20.19; P=0.006). Significant decreases were observed for both AZLI-BID and AZLI-TID compared with placebo groups. Time to first hospitalization and median days per number of patients hospitalized did not differ significantly between the treatment groups (Days 0–84). Weight increased 0.77% for the AZLI-pooled group compared with placebo (Day 28: 95% CI, 0.00–1.55; P 5 0.051).
Retsch-Bogart et al.[78] (2009) AIR-CF1 Aztreonam inhalation solution 75 mg TID for 28 days (AZLI) vs placebo	RCT, DB, PC, MC Patients ≥6 years of age with cystic fibrosis, FEV_1 >25% and <75%, *Pseudomonas aeruginosa* (PA) airway infection, and no recent use of antipseudomonal antibiotics or azithromycin	N=164 42 days	Primary: Change in symptoms Secondary: Changes in pulmonary function, hospitalizations, nonrespiratory CFQ-R scales, sputum PA density	Primary: The adjusted mean CFQ-R-Respiratory scores increased for AZLI-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 9.7 points; 95% CI, 4.3 to 15.1; P<0.001). Two weeks after treatment, CFQ-R-Respiratory scores had declined but remained above baseline values for AZLI-treated patients, and had continued to decline for placebo-treated patients (day 42 treatment difference, 6.3 points; 95% CI, 1.2 to 11.4; P<0.015). Secondary: The adjusted mean FEV_1 increased for AZLI-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 10.3%; 95% CI, 6.3 to 14.3; P<0.001). Two weeks after treatment, the mean FEV_1 had declined but remained

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				above baseline for AZLI-treated patients, and had continued to decline for placebo-treated patients (day 42 treatment difference, 5.7%; 95% CI, 2.1 to 9.4; P<0.002). The adjusted mean relative change in FEV% predicted values also increased for AZLI-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 10.2%; 95% CI, 6.2 to 14.2; P<0.001) and declined for both groups after treatment (day 42 treatment difference, 5.7%; 95% CI, 2.0 to 9.4; P=0.003). The adjusted mean sputum PA density decreased for AZLI-treated patients and remained near baseline for placebo-treated patients (day 28 treatment difference, -1.453 $\log_{10}$ cfu/g; 95% CI, -2.1 to -0.8; P<0.001). Two weeks after treatment (day 42), values were near baseline values for both treatment groups (P=0.822). There was a trend toward fewer hospitalized patients in the AZLI group (5%) than in the placebo group (14%; days 0 to 42; P=0.064) and toward fewer mean hospitalization days (AZLI group, 0.5 days; placebo group, 1.5 days; P=0.049). Weight increased 1.1% for the AZLI-treated group and 0.1% for the placebo-treated group (day 28: 95% CI, 0.33 to 1.69; P=0.004). The responses of AZLI-treated patients were significantly larger than those of placebo-treated patients for 6 of the 11 nonrespiratory CFQ-R scales; these scales included Eating, Emotional Functioning, Health Perceptions, Physical Functioning, Role Limitation/School Performance, and Vitality.
Oermann et al.[75] (2010) AIR-CF3 Aztreonam inhalation solution 75 mg BID to TID	OL Patients ≥6 years of age with cystic fibrosis and *Pseudomonas aeruginosa* (PA) airway infection,	N=274 18 months	Primary: Disease-related endpoints (change from baseline FEV_1% predicted, FEV_1 absolute volume, CFQ-R-Respiratory scores,	Primary: For treatment courses 1–9, percent change in FEV_1 (L) was positive at the end of each on-drug course. A greater response was observed for the TID regimen in general. The mean change in FVC from baseline ranged from -1.40% to 5.39% (BID) and from 0.97% to 6.18% (TID). The mean change in $FEF_{25–75}$ from baseline ranged from -4.20% to 16.05% (BID) and from -5.02% to 14.14%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 28 days (AZLI) Patients received up to nine courses (28 days on/28 days off) of 75mg AZLI two (BID) or three times daily (TID) based on randomization in the previous trials.	who previously participated in one of two Phase 3 studies (AIR-CF1 or AIR-CF2)		and density of PA in sputum	(TID). For the on-treatment months, the mean increase in CFQ-R-Respiratory score was >4. Changes on other symptom scales of the CFQ-R were consistent with treatment benefit. There was a greater improvement in the TID group than in the BID group. In the TID group, mean improvements from baseline for the Physical Functioning, Vitality and Health Perceptions domains tended to be greater during each of the intervals when the patient was on treatment and less during each of the intervals when the patient was off treatment. For the TID group, mean scores for the Weight domain tended to be above baseline throughout the nine treatment courses. Absolute changes from baseline for the remaining domains (emotional functioning, social functioning, body image, eating disturbances, role limitations/school performance and digestion) were variable and showed no apparent dose response. A total of 47.8% of patients were hospitalized at least once during the study. The median time to the first hospitalization for a respiratory event was 449 days, with median times of 431 and 449 days for the BID- and TID-treated groups, respectively. Median time to IV antipseudomonal antibiotics was 247 days (95% CI, 210 to 287), with similar times between the two regimen groups: 276 days for the BID-treated group (95% CI, 217 to 316) and 232 days for the TID group (95% CI, 179 to 288). Repeated courses of AZLI resulted in consistent weight gain, which were sustained over the 18-month period. Improvement was greater among patients receiving TID compared to BID treatment. Mean adherence was 92.0% in the BID group and 88.0% in the TID group.
Wainwright et al.[76] (2011)	RCT, DB, PC, MC Patients ≥6 years of	N=157 42 days	Primary: Change from baseline at Day 28	Primary: Adjusted mean change at Day 28 from baseline CFQ-R RSS scores was 3.22 for AZLI-treated and 1.41 for placebo-treated patients (treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aztreonam inhalation solution 75 mg TID for 28 days (AZLI) vs placebo	age with cystic fibrosis with an FEV_1 >75%, *Pseudomonas aeruginosa* (PA) airway infection, and who did not require immediate antipseudomonal antibiotic treatment of an impending exacerbation		on the CFQ-R RSS Secondary: Change from baseline at Days 14 and 42 on the CFQ-R RSS, change from baseline at Day 28 on the CFQ-R Physical Functioning Scale, use of additional antipseudomonal antibiotics, proportion of patients hospitalized, and change from baseline at Day 28 for log_{10} PA CFUs in sputum and FEV_1% predicted	effect 1.80; 95% CI: −2.83to 6.44; P=0.443). Secondary: Significant treatment effects favoring AZLI were observed for several secondary efficacy endpoints: change from baseline at Day 28 for adjusted mean log_{10} PA CFUs in sputum (AZLI: −1.4; placebo: −0.14; P=0.016) and adjusted mean relative change in FEV_1% predicted (AZLI: 0.29%; placebo: −2.5%; P=0.021). Amongst other efficacy endpoints, significant treatment effects favoring AZLI were observed for relative mean change from baseline FEV_1 (L) at Day 28 and CFQ-R Social Functioning scores. Use of oral, IV, or additional inhaled antibiotics was similar for the AZLI and placebo groups during the entire study, with most use occurring during the follow-up period for both treatment groups.
Bjornson et al.[28] (1993) Aztreonam 2 g IV every 8 hours plus clindamycin 600-900 mg every 8 hours vs aztreonam 2 g IV every 8 hours plus nafcillin 1.5-2 g IV	RCT, OL Patients with suspected aerobic gram-negative bacillary pneumonia or purulent bronchitis	N=84 Duration varied	Primary: Clinical response, bacteriologic response	Primary: Clinical response rates were reported as 83% in both aztreonam groups and the control group (P=0.951). The bacteriologic response was reported as 75% in the aztreonam groups and 63% in the control group (P=0.291).

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every 6 hours vs control group (amikacin plus mezlocillin or tobramycin plus ticarcillin)				
Réa-Neto et al.[51] (2008) Doripenem 500 mg IV every 8 hours vs piperacillin-tazobactam 4.5 grams IV every 6 hours Patients were switched to oral levofloxacin 750 mg once daily after receiving IV study drug for at least 72 hours.	PRO, RCT, OL, MC Patients aged 18 years or older with signs and symptoms of nosocomial pneumonia, including non-ventilated patients and those with early-onset ventilator-associated pneumonia	N=448 7-14 days	Primary: Clinical cure rate in the clinically evaluable population and in the cMITT population Secondary: Clinical cure rate at the end of IV therapy and at the LFU visit, clinical and microbiological cure rates in the microbiologically evaluable patients at the TOC visit and in the mMITT population, clinical and microbiological cure rates at the TOC visit in microbiologically evaluable patients with early-onset	Primary: The clinical cure rates in clinically evaluable patients at the TOC visit were 81.3% in the doripenem arm and 79.8% in the piperacillin/tazobactam arm (95% CI, -9.1 to 12.1). In the cMITT population, the clinical cure rates in the doripenem and piperacillin/tazobactam arms were 69.5% and 64.1%, respectively (95% CI, -4.1 to 14.8). Secondary: Clinical response rates at the end of IV study drug therapy in clinically evaluable patients were 87% in both treatment arms (95% CI, -9.2 to 9.2%). Clinical relapse rates at the LFU visits were low for both the doripenem (3%) and piperacillin/tazobactam (4%) treatment arms. The clinical cure rates in microbiologically evaluable patients at the TOC visit were 82.1% and 78.3% (95% CI, -9.4 to 17.1) in the doripenem and piperacillin/tazobactam arms, respectively. In the mMITT population, clinical cure rates were 67.6% and 67.4%, respectively (95% CI, -11.4 to 11.9). Microbiological responses in the microbiologically evaluable patients at the TOC visit were achieved in 84.5% of patients in the doripenem arm and 80.7% of patients in the piperacillin/tazobactam arm (95% CI, -8.9 to 16.5).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			VAP, and all-cause mortality at day 28 in the cMITT population.	The all-cause mortality at day 28 in the cMITT population was 13.8% with doripenem and 14.6% with piperacillin/tazobactam (95% CI, -7.9 to 6.3%). A Kaplan-Meier analysis found no difference in cumulative mortality rate between the two treatment arms.
Chastre et al.[50] (2008) Doripenem 500 mg IV every 8 hours vs imipenem 500 mg IV every 6 hours or 1,000 mg every 8 hours	RCT, MC, AC, OL Adults meeting clinical and radiologic criteria for ventilator-associated pneumonia	N=531 7-14 days	Primary: Clinical cure rates in the clinically evaluable and cMITT populations Secondary: Clinical cure rates in the mMITT, microbiological cure rates in the microbiologically evaluable population; clinical relapse rates at the LFU visit; per-pathogen clinical/ microbiological cure rates; emergence of *P. aeruginosa* strains acquiring decreased susceptibility to study drug; emergent infection rate; all-cause mortality	Primary: Clinical cure rates were 68.3% (doripenem) and 64.2% (imipenem) in the clinically evaluable (95% confidence interval, -7.9% to 10.3%) and 59.0% (doripenem) and 57.8% (imipenem) in the cMITT populations (95% confidence interval, -9.1% to 16.1%). Secondary: In the microbiologically evaluable patients, favorable microbiological response rates were 73.3% with doripenem and 67.3% with imipenem (95% confidence interval, -6.8% to 18.8%). The per-pathogen clinical and microbiological cure rates in the microbiologically evaluable population for *S. aureus* (methicillin-susceptible), *E. cloacae*, *Escherichia coli*, *K. pneumoniae*, *H. influenzae*, and *P. aeruginosa* were generally higher with doripenem than with imipenem; however, sample sizes were small. In patients with *Pseudomonas aeruginosa*, clinical cure was 80.0% (doripenem) and 42.9% (imipenem) (P=NS); microbiological cure was 65.0% (doripenem) and 37.5% (imipenem). The all-cause mortality at day 28 in the cMITT population was 10.8% with doripenem and 9.5% with imipenem (95% confidence interval -4.4% to 7.0%). The incidence and types of all adverse events and those considered drug-related by the investigators were similar in both treatment groups.
Friedland et al.[29] (2004) Ertapenem 1 g IV	RCT, MC, DB Patients 18 years of age and older with	N=857 7-14 days post-therapy	Primary: Clinical response at the test-of-cure (TOC) visit,	Primary: At the TOC visit, the combined response rates were 90% in patients with chronic obstructive pulmonary disease (COPD) and 93% in patients without COPD.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs ceftriaxone 1 g IV daily Patients with clinical improvement meeting pre-specified criteria could be switched to oral amoxicillin-clavulanate or other oral antimicrobial based on pathogen susceptibility for a total of 10-14 days.	typical community-acquired pneumonia admitted to the hospital for parenteral antimicrobial therapy		clinical response at the completion of parenteral therapy	In the patients without COPD, favorable results were seen in 93% of both ertapenem and ceftriaxone patients. There were no significant differences between treatment groups (P=0.94) or between patients with and without COPD (P=0.17). Clinical response at the completion of parenteral therapy was seen in 95% of ertapenem patients and 94% of ceftriaxone patients.
Yanagihara et al.[52] (2006) Imipenem-cilastatin 0.5 g twice daily vs ampicillin-sulbactam 3 g twice daily	RCT, PRO Elderly patients >65 years old with moderate-to-severe community-acquired pneumonia	N=67 7-14 days	Primary: Clinical efficacy Secondary: Bacteriological efficacy, adverse events	Primary: Overall clinical efficacy of ampicillin/sulbactam therapy was 91.4% compared to 87.5% for imipenem/cilastatin therapy (P=NS). Secondary: The eradication rate of *S. pneumoniae*, *MSSA*, and *H. influenzae* was 100% in both treatment arms (P=NS). The overall eradication rate for the pathogenic microorganism was 84% in the ampicillin/sulbactam group and 80%in the imipenem/cilastatin group (P=NS). All adverse reactions were mild or moderate and transient in both treatment groups.
Romanelli et al.[30] (2002) Imipenem-cilastatin	MC, OL, PRO, RCT Patients from 70-94	N=204 Duration of study varied	Primary: Satisfactory clinical response (complete	Primary: A satisfactory clinical and bacteriological response was achieved in 86.3% of the imipenem-cilastatin group, 86.5% of the meropenem group, 69% of the ceftriaxone and clarithromycin group and 85.7% of the clarithromycin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
500 mg IV TID for 8-14 days vs meropenem 500 mg IV TID for 7-13 days vs clarithromycin 500 mg IV and ceftriaxone 1 g IV BID for 9-16 days vs clarithromycin 500 mg IV and amikacin 250 mg IV BID for 7-14 days	years of age admitted to hospital with community-acquired pneumonia (CAP)	from 13 to 16 days	remission or attenuation of all systemic and local signs and symptoms of infection without use of another antibiotic) and bacteriological response (eradication of the primary pathogen[s]) at the end of treatment. Secondary: Normalized or improved radiological exam, mean time to normalization of body temperature	and amikacin group. Secondary: There was no significant difference in the normalization or improvement in radiological exams between the groups. The mean time to normalization of body temperature was 4.7 days in the imipenem-cilastatin group, 4.2 days in the meropenem group, 5.4 days in the ceftriaxone and clarithromycin group and 5.1 days in the clarithromycin and amikacin group.
Bartoloni et al.[31] (1999) Imipenem-cilastatin 2 g IV QD vs meropenem 1.5 g IV QD	RCT, MC Individuals aged 18-94 years of age with community-acquired pneumonia (CAP)	N=144 9-10 days	Primary: Clinical efficacy (cure or improvement in signs and symptoms) Secondary: Bacteriological response (either presumed or confirmed eradication of all pathogens) and	Primary: At the end of therapy, clinical response was observed in 90.9% of the patients receiving imipenem-cilastatin and 89.1% of meropenem-treated patients. In patients who were followed up for 2-4 weeks, the response was satisfactory (100%) for both treatments. Secondary Response was considered satisfactory in 100% of the meropenem group and 92.9% in the imipenem-cilastatin group and at follow-up; it was 100% for both treatments. Drug-related adverse events were reported in 4.2% of the meropenem-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			safety assessment	treated patients and in 11.0% of the imipenem-cilastatin-treated patients.
Schmitt et al.[53] (2006) Imipenem-cilastatin 4 g/500 mg every 8 hours vs piperacillin-tazobactam 1 g/1 g every 8 hours Additional aminoglycoside therapy was mandatory if *Pseudomonas aeruginosa* was present.	RCT, DB, MC Hospitalized patients with nosocomial pneumonia	N=221 5-21 days	Primary: Clinical response at the end of the treatment period Secondary: Clinical responses on the last day of treatment or on day 21 and on day 14 ± 7 days after treatment, bacteriological responses, safety	Primary: Therapeutic response was seen in 66% [95% CI, 56.5%–75%] of patients receiving piperacillin/tazobactam and in 70% [95% CI, 60.4%–78.2%] of patients receiving imipenem/cilastatin. Failure rates were similar at 18.7% and 18.2%, respectively. On the last day of treatment or on day 21, therapeutic responses were higher and seen in 71% [95% CI, 61.3%–79.2%] and 77.3% [95% CI, 68.1%–84.5%] of patients receiving piperacillin/tazobactam and imipenem/cilastatin respectively. Failure rates were 17.8% and 16.4% respectively. Secondary: At the second follow-up (14 ± 4 days after the end of treatment) clinical responses were 59.8% [95% CI, 49.9%–69%] and 66.4% [95% CI, 56.6%–74.9%] and failure rates were 19.6% and 15%, in patients receiving piperacillin/tazobactam and imipenem/cilastatin respectively. The majority of patients in both groups responded to treatment and the overall response rate was similar for the two agents. Failure rates were also similar for the two treatment groups at each of the observation periods. Eradication immediately after treatment with piperacillin/tazobactam or imipenem/cilastatin was 45.7% and 52.7%, respectively compared with 40.3% and 50% at the first follow-up and 34.6% and 42.2% at the second follow-up, respectively. Overall, 74.5% and 64.9% of patients receiving piperacillin/tazobactam and imipenem/cilastatin, respectively reported adverse events, the majority of which were of mild intensity. The most common related adverse events were diarrhea and fever in the piperacillin/tazobactam group and increased alkaline phosphatase, nausea and vomiting in the imipenem/cilastatin group.
Joshi et al.[54] (2006) Imipenem-cilastatin 500 mg IV every 6	RCT, DB, MC Hospitalized patients with acute nosocomial	N=437 21 days	Primary: Clinical cure and microbiological response rates; pathogen	Primary: The overall clinical cure rate was 68% in P/T patients and 61% in IMP patients in the EE population (P = 0.256). Microbiological response rates were comparable among EE patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours (IMP) vs piperacillin-tazobactam 4.5 grams IV every 6 hours (P/T) Patients also received aminoglycoside therapy	pneumonia		eradication rates; length of hospital stay; hospital readmissions; adverse events	treated with P/T and those treated with IMP. Microbiological responses for P/T and IMP patients were: eradication, 64% versus 59%; persistence, 29% versus 21%; relapse, 0% versus 5%; and superinfection, 7% versus 15%, respectively. Gram-positive isolates were eradicated in 83% of P/T patients and 75% of IMP patients; Gram-negative pathogens were eradicated in 72% of P/T patients and 77% of IMP patients. P/T and IMP patients had similar hospital and ICU length of stay. Hospital readmission rates in both groups were small and were not significantly different. There were no significant differences in adverse events between the two treatment groups.
Ito et al.[83] (2010) Imipenem-cilastatin 1 g IV every 12 hours for 7 to 14 days (IPM/CS) vs piperacillin-tazobactam 5 g IV every 12 hours for 7 to 14 days (TAZ/PIPC)	RCT, OL, SC Patients aged ≥15 years of age with a risk for aspiration who had been hospitalized after developing moderate-to-severe pneumonia in the community or nursing home	N=469 30 days	Primary: Clinical response rate at the end of treatment (EOT) in validated per protocol (VPP) population Secondary: Clinical response during treatment (days 4 and 7) and at the end of study (EOS) in VPP population, and survival at day 30 in modified intention-to-treat (MITT) population	Primary: At the EOT visit, the clinical effective rate for the VPP population was 83% for TAZ/PIPC and 82% for IPM/CS (P=0.92). Secondary: There were no significant differences between the groups in any of the secondary outcome measures. Mortality rate within 30 days of admission in MITT population was 15% in the TAZ/PIPC group and 24% in the IPM/CS group (P=0.12). The most frequent adverse event was diarrhea in both groups, affecting 28% of patients receiving TAZ/PIPC and 31% of patients receiving IPM/CS.
Freire et al.[71] (2010)	DB, RCT, MC Patients ≥18 years	N=945 7 to 14 days	Primary: Clinical response in clinically	Primary: In the CE population at the TOC visit, 67.9% of patients receiving TGC and 78.2% of patients receiving IMI/CIL were considered cured. In the c-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Imipenem-cilastatin 500 mg to 1g IV every 8 hours plus vancomycin 1g every 12 hours for MRSA (IMI/CIL) vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours plus ceftazidime 2 g IV every 8 hours if needed for *P. aeruginosa*	of age with hospital-acquired pneumonia		evaluable (CE) and clinical modified intent to treat (c-mITT) populations at the test-of-cure (TOC) visit, safety	mITT population, 62.7% of patients receiving TGC and 67.6% of patients receiving IMI/CIL were considered cured. TCG was found to be non-inferior to IMI/CIL in the c-mITT population (P=0.001; 95% CI, -11.0 to 1.3), but not in the CE population (P=0.120; 95% CI -17.8 to -3.0). Patients with ventilator-associated pneumonia (VAP) had lower cure rates at the TOC visit than non-VAP patients in both treatment groups. For patients with VAP, the cure rate for TGC was 47.9% in the CE population and 46.5% in the c-mITT population. The cure rate for IMI/CIL was 70.1% in the CE population and 57.8% in the c-mITT population. For patients with non-VAP, the cure rate for TGC was 75.4% in the CE population and 69.3% in the c-mITT population. The cure rate for IMI/CIL was 81.3% in the CE population and 71.2% in the c-mITT population. Treatment-emergent adverse events (TEAEs) were reported by 78% in all patients, with no significant differences between the 2 treatment groups (P=1.000). The most commonly reported TEAEs were diarrhea, nausea, and vomiting. TGC patients had significantly more nausea (15.4%) and vomiting (12.6%) than patients receiving IMI/CIL (P<0.001). Patients receiving IMI/CIL had a significantly greater frequency of diarrhea (15%) than TGC (P<0.05). Reports of 1 or more serious adverse event (SAE) revealed no statistical difference among both therapies (P=0.940), but more IMI/CIL patients (11.6%) reported respiratory system SAEs vs TGC patients (7.1%). Overall mortality did not differ between the TCG (14.1%) and IMI/CIL (12.2%). More deaths occurred in VAP patients treated with TGC than IMI/CIL.
Miscellaneous Infections				
Kobayashi et al.[74] (2009) Aztreonam 150 mg/kg/day plus ampicillin-sulbactam 150	RCT Pediatric patients with hematologic disease and solid tumor with febrile neutropenia	N=54 (177 episodes) 120 hours	Primary: Treatment success	Primary: Success rates were 57.1% and 62.5% in the PIPC/TAZ+CAZ and SBT/ABPC+AZT groups, respectively (P≥0.05). There were 2 deaths in the PIPC/TAZ+CAZ group. The patients died within 48 hours from onset of the febrile episode.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/day divided into 4 doses (SBT/ABPC+AZT) vs ceftazidime 100 mg/kg/day plus piperacillin-tazobactam 125 mg/kg/day divided into 4 doses (PIPC/TAZ+CAZ) Treatment was continued until completion of the appropriate course of therapy for a defined clinical or microbiologic infection.				The success rates in episodes with absolute neutrophil counts <0.5x10^9/L at the end of treatment were 70.0% and 74.1% in the PIPC/TAZ+CAZ and SBT/ABPC+AZT groups, respectively, and the success rates in bacteremia episodes were 50% in both groups. The percentages of episodes with new infections were 25.7% and 20.3%, respectively. Duration of fever and antibiotic therapy did not differ between the groups, and no major adverse effects occurred in the study.
Paul et al.[35] (2006) Carbapenems, cefepime, ceftazidime, or piperacillin-tazobactam monotherapy with or without vancomycin	MA Patients with febrile neutropenia	N=5,769 (33 trials) Variable duration	Primary: All-cause mortality 30 days posttreatment Secondary: Treatment failure (non-resolved infection, treatment modification or death owing to infection; infection-related mortality;	Primary: There was no significant difference in all cause mortality between the carbapenems and comparative medications. Imipenem was compared to ceftazidime and cefepime in 4 trials each, with cefoperazone-sulbactam* in 3 trials and with piperacillin-tazobactam in 1 trial, while meropenem was compared with ceftazidime in 5 trials, cefepime in 2 trails and piperacillin in 1 trial (RR, 0.93; 95% CI: 0.68 to 1.29). Major comparison was with ceftazidime (RR, 0.91; 95% CI: 0.54 to 1.54, 8 studies, 2028 participants). Cefepime was compared with ceftazidime in 8 trials, imipenem in 4, piperacillin-tazobactam in 3 and meropenem in 2 trials. All-cause mortality was significantly higher with cefepime compared to other β-lactams (RR, 1.44; 95% CI: 1.06 to 1.94, P=0.02). In 4 studies, only children were assessed and mortality was higher with cefepime compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			treatment modifications assessing; failure to eradicate causative pathogen(s); superinfection; adverse events)	to ceftazidime (RR, 2.28; 95% CI: 0.53 to 9.79, 3 studies, 263 participants) and equal in the 1 study comparing it with meropenem. Piperacillin-tazobactam was compared to cefepime in 4 trials and imipenem and meropenem in 1 trial each. All-cause mortality was observed in 4 trials (RR, 0.62; 95% CI: 0.34 to 1.13) and an advantage was found with piperacillin-tazobactam compared to other β-lactams. Secondary: Comparing carbapenems to other β-lactams, most often ceftazidime, for treatment failure, there was an advantage found for carbapenems (RR, 0.86; 95% CI: 0.80 to 0.94), for antibiotic modifications (RR, 0.86; 95% CI: 0.79 to 0.94) and for glycopeptides addition (RR, 0.70; 95% CI: 0.57 to 0.86). There was no significant difference found with the additional of an antifungal (RR, 1.14; 95% CI: 0.94 to 1.38). There was no significant discernable benefit regarding infection-related mortality (RR, 0.85; 95% CI: 0.51 to 1.41), microbial failure (RR, 0.98; 95% C: 0.88 to 1.09) and superinfections (RR, 0.89; 95% CI: 0.71 to 1.12). Meta-analysis of the 3 trials comparing imipenem with cefoperazone-sulbactam was consistent with the above findings except for failure with modification, which was more frequent with imipenem, but not significant (RR, 1.19; 95% CI: 0.99 to 1.43). More frequent side effects were observed with imipenem (RR, 1.72; 95% CI: 1.45 to 2.04, 8 studies, 1,419 patients) including seizure (RR, 2.78; 95% CI: 1.00 to 7.76, 7 studies, 1,885 participants), than other β-lactams. In general carbapenems were associated with more episodes of pseudomembranous colitis than cephalosporins (RR, 1.94; 95% CI: 1.24 to 3.04). No significant difference was observed when comparing cefepime to other β-lactams with regards to treatment failure (RR, 1.03; 95% CI: 0.96 to 1.10, 16 trials). Infection-related mortality was observed in 13 trials (RR, 1.24; 95% CI: 0.78 to 1.97), microbiological failure and need for drug modifications were equivalent and superinfections were more prevalent with cefepime (RR, 1.70; 95% CI: 0.94 to 3.09).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Infection-related mortality was lower with piperacillin/tazobactam compared to other β-lactams (RR, 0.52; 95% CI: 0.22 to 1.23, 4 trials). Treatment failure and other outcomes were similar among groups.
Milsom et al.[59] (1998) Cefotetan 2 g IV as a single dose vs alatrofloxacin 200 mg IV as a single dose	RCT, MC, DB Hospitalized patients 18 years and older undergoing elective colorectal surgery	N=317 30 days	Primary: Clinical response rates	Primary: The incidence of primary wound infections (primary surgical-site infections, intra-abdominal infections, bacteremia, and fever of unknown origin) that occurred up to 30 days after surgery was comparable between the alatrofloxacin and cefotetan groups at the time of hospital discharge (21% vs 18%) and at the end of the study (28% in each group). All treated patients in the alatrofloxacin and cefotetan groups were comparable with respect to remote-site infections (Pneumonia, urinary tract infection, bacteremia unrelated to surgery, or other infection) up to the time of hospital discharge (8% vs 10%) and by day 30 (7% vs 5%). The percentages of patients with clinically significant laboratory abnormalities were similar between the two treatment groups.
Noyes et al.[60] (1998) Cefotetan vs cefazolin vs ampicillin-sulbactam	RCT Women undergoing cesarean section who had either experienced labor for a duration of ≥6 hours or rupture of amniotic membranes	N=293 Single dose study	Primary: Incidence of postpartum endomyometritis	Primary: The incidence of postpartum endomyometritis was 7.4% following the ampicillin/sulbactam regimen, 14.3% after the cefazolin regimen, and 11.1% after the cefotetan regimen. There was no significant difference in postpartum infection among the three study arms. The incidence of endomyometritis in the three single-dose study arms was not higher than previously noted in studies where three doses of antibiotic were administered.
Bracero[61] (1997) Cefotetan 1 g IV as a single dose	SC, RCT Hospitalized pregnant women who were to undergo cesarean	N=170 Single dose study	Primary: Prevention of postoperative infection following cesarean delivery and adverse events	Primary: Successful prophylaxis was reported in 79% of patients receiving ampicillin/sulbactam and in 72% patients receiving cefotetan. There were no statistically significant differences in the rates of endometritis or urinary tract infections between the two treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ampicillin-sulbactam 1 g IV as a single dose	delivery and who were at high risk of developing postoperative infection			The mean duration of hospitalization was 5.5 days for patients receiving ampicillin/sulbactam and 5.7 days for patients receiving cefotetan.
Liberman et al.[63] (1995) Cefotetan 2 g IV as a single dose preoperatively (group 1) vs cefoxitin 2 g IV as a single dose preoperatively (group 2) vs cefoxitin 2 g IV as a single dose preoperatively followed by 3 doses postoperatively (group 3)	RCT, DB Patients with nonperforated acute appendicitis undergoing appendectomy	N=136 Single dose study	Primary: Wound infection rates	Primary: The overall wound infection rate was 4.4%. No post-operative infections were found in group 1, 11.1% occurred in group 2, and 1.9% occurred in group 3. There was no significant difference between groups 1 and 3; however, there were significant differences in infections rates between groups 1 and 2 (P=0.04) and groups 2 and 3 (P=0.05).
Hemsell et al.[62] (1995) Cefotetan 1 g IV as a single dose vs	PRO, RCT, DB, Women undergoing elective abdominal hysterectomy	N=511 Single dose study	Primary: Prevention of major operative site infections	Primary: A major operative site infection requiring parenteral antimicrobial therapy developed in 9% of evaluable women: 11.6% of women given cefazolin prophylaxis and 6.3% of women given cefotetan prophylaxis (RR, 1.84; 95% CI, 1.03 to 3.29; P<0.05). Risk factors for major operative site infection were younger age, lower postoperative hemoglobin concentration, and a proliferative endometrium.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cefazolin 1 g IV as a single dose				Of the women given cefazolin prophylaxis, 3.9%had a postoperative pelvic abscess compared with 0.8% of women given cefotetan prophylaxis (RR, 4.9; 95% CI, 1.09 to 22.16; P =0.04). A greater number of infections and more serious infections occurred following cefazolin prophylaxis; this treatment resulted in 234 additional hospital days for administration of IV antimicrobial therapy.
Jeong et al.[77] (2010) Cefotetan 2 g IV on the day of the operation, then 1 g IV on postoperative days 1 to 3 (group B) vs cefazolin, gentamicin and metronidazole IV at 8 hour intervals until postoperative day 5 (group A)	OL Patients undergoing elective surgery for primary colorectal cancer	N=461 30 days	Primary: Treatment failure	Primary: The overall morbidity rate was 5.4% and the overall treatment failure rate was 3.3%. The treatment failure rates were 3.1% in Group A and 3.4% in Group B (P=0.866). The mean length of stay and postoperative morbidity were similar for both groups. The overall surgical-site infection (SSI) rate was 2.8%, and this was the most common reason for treatment failure in both groups. The SSI rates were similar for the two groups (2.7% in Group A and 3.0% in Group B; P=0.846).
Roy et al.[65] (1998) Cefoxitin 2 g IV prior to hysterectomy vs trovafloxacin 200 mg PO prior to	RCT, DB Women 18 years of age and older who were scheduled for an elective vaginal or abdominal hysterectomy for nonmalignant disease	N=363 30 days	Primary: Prophylactic success at 30 days Secondary: Time to development of an infection, duration of postoperative fever, duration of postoperative	Primary: At the end of the study, the prophylactic success rates were 88% in the trovafloxacin group and 91% in the cefoxitin group (P=0.608). Secondary: The time to development of an infection was 7.9 days in the trovafloxacin group compared to 10.3 days in the cefoxitin group. The duration of postoperative fever was 0.6 days in the trovafloxacin group and 0.77 days in the cefoxitin group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hysterectomy			hospitalization	The duration of postoperative hospitalization was 3.8 days in the trovafloxacin group compared to 3.9 days in the cefoxitin group.
Kow et al.[26] (1995) Cefoxitin 2 g IV on induction of anesthesia vs cefotaxime 1 g plus metronidazole 500 mg IV on induction of anesthesia vs cefoxitin 2 g IV on induction of anesthesia plus another 2 g at 6 and 12 hours postoperatively vs cefotaxime 1 g plus metronidazole 500 mg IV on induction of anesthesia followed by cefotaxime 1 g at 6 and 12 hours postoperatively	RCT, MC Patients 16 years of age and older admitted to the hospital for all types of intra-abdominal surgery	N=1,010 4-6 weeks post-operation	Primary: Incidence of wound infections, length of hospital stay	Primary: Wound infections were diagnosed in 5.7% of all patients. The incidence of wound infections was not significantly different between treatment groups (P>0.19). There was no significant difference in length of hospital stay between the treatment groups.
Lucasti et al.[55] (2008)	RCT, MC, DB	N=476	Primary: Clinical	Primary: Doripenem and meropenem were associated with clinical cure rates at the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doripenem 500 mg IV every 8 hours vs meropenem 1 gram IV every 8 hours Patients could be switched to oral amoxicillin-clavulanate after a minimum of 9 doses and adequate clinical improvement.	Hospitalized adult patients with complicated intra-abdominal infections (cIAIs)	21-60 days	cure rate at the TOC visit (21–60 days after the last dose of study drug) and the clinical cure rate in the microbiological modified ITT (mMITT) population Secondary: Clinical cure rates at the EOT (IV), early follow-up, and TOC visits	TOC visit of 85.9% and 85.3%, respectively (95% CI, -7.7% to 9.0%). In the mMITT population, the clinical cure rates were 77.9% and 78.9%, respectively (95% CI, -9.7% to 7.7%). Secondary: Clinical cures assessed in the clinically evaluable and microbiologically evaluable population at the EOT (IV), early follow-up, and TOC visits were not significantly different within or between populations of doripenem and meropenem. The proportions of patients experiencing adverse events were not significantly different between the 2 treatment arms (83.0% vs 78.0%).
Namias et al.[56] (2007) Ertapenem 1 gram IV once daily vs piperacillin-tazobactam 3.375 grams IV every 6 hours	RCT, MC, DB Patients 18 to 90 years of age with presumptive (pre-operative) or confirmed complicated intra-abdominal infections	N=500 4-14 days	Primary: Clinical response rates Secondary: Microbiological efficacy, clinical failure, mortality	Primary: Favorable clinical responses were demonstrated for 82.1% of the patients in the ertapenem group and 81.7% of the patients in the piperacillin/tazobactam group (95% CI -9.6, 10.5). At the end of therapy, 89.6% and 86.2%, and at LFA, 78.9% and 79.3%, of the microbiologically evaluable patients had favorable clinical responses in the ertapenem and piperacillin/tazobactam treatment groups, respectively. Clinical response rates of 63.2% for ertapenem and 60.9% were similar for piperacillin/tazobactam-treated patients in the MITT population at EFA (95% CI -7.5, 12.0). Secondary: There were no clinically important differences in the response rates of gram-positive, gram-negative, or anaerobic pathogens in the ertapenem and piperacillin/tazobactam treatment groups. Favorable overall microbiological responses were demonstrated in 82.2% in the ertapenem group and 82.5% in the piperacillin/tazobactam group (95% CI -10.1, 9.8)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				at EFA. The pathogens isolated most frequently were *Escherichia coli, Bacteroides fragilis*, and *Bacteroides thetaiotaomicron*. At EFA, there were 22 clinical failures (17.9%) in the ertapenem group and 20 (18.5%) in the piperacillin/tazobactam group. The incidence of adverse events and study discontinuations because of adverse events was similar in the two groups. During the study and post-treatment follow-up period, clinical adverse events resulted in 21 deaths, nine of which occurred in the ertapenem group (3.6%) and 12 in the piperacillin/tazobactam group (4.9%; relative risk 0.75 [95% CI 0.30, 1.77]; risk difference -1.21[95% CI -5.08, 2.53]).
Yellin et al.[57] (2007) Ertapenem 1 gram IV once daily (13-17 years of age) or 15 mg/kg (2 to 12 years of age) vs ticarcillin-clavulanate 50 mg/kg 4 to 6 times daily (<60 kg) or 3.1 grams 4 to 6 times daily (≥60 kg)	RCT, MC, OL Children aged 3 months to 17 years of age with complicated intra-abdominal infections (cIAI) or acute pelvic infections	N=105 3-9 days	Primary: Incidence of any serious drug-related clinical and/or laboratory adverse experiences Secondary: Overall response rates, drug-related clinical and/or laboratory adverse experiences, incidence of moderate-to-severe administration site reactions,	Primary: Forty-six percent of patients had 1 or more clinical adverse event as assessed by the investigator: 39% in the ertapenem group and 67% in the comparator group. Eleven patients (14%; 95% CI, 7.0 –23.0) in the ertapenem group and 8 patients (33%; 95% CI, 15.6 –55.3) in the comparator group reported drug-related clinical and/or laboratory adverse experiences. Infusion site pain was the most common drug-related adverse event in both groups. Secondary: Overall response rates were 89% for ertapenem and 73% for the comparator. Comparable rates were seen across each of the age groups studied. In the modified intent-to-treat analysis, the age-adjusted posttreatment clinical response rates were 87% and 100% in the cIAI and API patients, respectively, for ertapenem and 73%and 100%, respectively, for ticarcillin/clavulanate.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall age-adjusted response rates were 91% for ertapenem and 83% for the comparator. Eleven percent (95% CI, 5.2–20.0) in the ertapenem group and 25% (95% CI, 9.8–46.7) in the comparator group experienced ≥1 local reactions of any intensity at the infusion/injection site.
Falagas et al.[58] (2008) Ertapenem vs piperacillin-tazobactam, ceftriaxone plus metronidazole, or ticarcillin-clavulanic acid	MA Patients with complicated intra-abdominal (cIAI) infections or acute pelvic infections (API)	7 trials 4-14 days	Primary: Clinical success Secondary: Mortality, laboratory adverse events, patient withdrawals because of adverse events	Primary: No difference was found regarding clinical success in patients treated with ertapenem, compared to those treated with other antibiotics (OR: 1.11, 95% CI, 0.89–1.39). There was no difference in microbiological success of adult patients with cIAIs treated with ertapenem compared to those treated with comparator antibiotics (OR: 1.19, 95% CI: 0.83–1.71). Microbiological or clinical success did not differ between compared treatments for the subsets of patients infected with either *P. aeruginosa* (OR: 1.00, 95% CI: 0.41–2.45) or *Enterococcus* spp. (OR: 1.19, 95% CI: 0.60–2.39). Secondary: There was no difference in mortality between adult patients with cIAIs treated with ertapenem or comparator antibiotics (OR: 1.14, 95% CI: 0.72–1.83). No difference was found regarding clinical adverse events between adult patients with cIAIs treated with ertapenem compared to those treated with other antibiotics (OR: 0.86, 95% CI: 0.61–1.20). Significantly more laboratory adverse events were noted in patients with cIAIs, treated with ertapenem compared to patients treated with other antibiotics (OR: 1.73, 95% CI: 1.14–2.61). No difference was found regarding withdrawals from the included studies because of adverse events, between patients with cIAIs treated with ertapenem compared to those treated with other antibiotics (OR: 0.94, 95% CI: 0.47–1.87).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Itani et al.[41] (2006) Ertapenem vs cefotetan	RCT, DB Patients undergoing elective colorectal surgery	N=1,002 4 weeks	Primary: Absence of surgical-site infection, anastomotic leakage, or antibiotic use 4 weeks postoperatively	Primary: The rate of overall prophylactic failure was 40.2% in the ertapenem group and 50.9% in the cefotetan group in the ITT analysis (95% CI, -17.1 to -4.2). The rate of overall prophylactic failure was 28.0% in the ertapenem group and 42.8% in the cefotetan group in the per-protocol analysis (95% CI, -21.9 to -7.5). The most common reason for failure of prophylaxis in both groups was surgical-site infection: 17.1% in the ertapenem group and 26.2% in the cefotetan group (95% CI, -14.4 to -3.7). In the treated population, the overall incidence of *Clostridium difficile* infection was 1.7% in the ertapenem group and 0.6% in the cefotetan group (P=0.22).
Gesser et al.[36] (2003) Ertapenem 1 g IV or IM daily vs ceftriaxone 1 g IV or IM daily vs piperacillin-tazobactam 3.375 mg IV every 6 hours	RCT, DB, MC Patients ≥18 years of age with a complicated urinary tract infection (CUTI), complicated intra-abdominal infection, acute pelvic or complicated skin/skin structure infection, or community-acquired pneumonia (CAP)	N=3,255 Up to 21 days	Primary: Clinical response at the test-of-cure (TOC) visit for intra-abdominal, skin/skin structure, pelvic infections, and CAP, and microbiological response at TOC for CUTI	Primary: Clinical cure rates in patients with deep tissue infections (intra-abdominal, pelvic, or skin/skin structure) were 84.8% in the ertapenem group and 82.8% in the piperacillin-tazobactam group, and no significant difference was seen between groups. Clinical cure rates in patients with CAP were 95.0% in the ertapenem group and 88.9% in the ceftriaxone group. Microbiological response in patients with CUTI was 90.5% in the ertapenem group and 92.0% in the ceftriaxone group, and no significant difference was seen between groups.
Arguedas et al.[64] (2009) Ertapenem 1 gm IV	RCT, DB, AC Patients ≥3 months and <18 years with	N=404 14 days	Primary: Incidence of clinical and laboratory drug-	Primary: In each group, the mean duration of therapy (Parenteral and oral antibiotic therapy) was 11 days and the median duration of parenteral therapy (ertapenem or ceftriaxone) was 4 days.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
as a single daily dose (children aged 13-17 years) or 30 mg/kg/day divided twice daily (children aged 3 months to 12 years) vs ceftriaxone 50 mg/kg/day as a single dose (children aged 13–17 years) or 50 mg/kg/day divided twice daily (children aged 3 months to 12 years)	complicated urinary tract infections, skin and soft-tissue infections and community-acquired pneumonia requiring initial parenteral antibiotic therapy		related serious adverse events (AEs) Secondary: Incidence of any drug-related AEs and any moderate-to-severe reactions at the parenteral infusion site	Overall, 46.7% of the children had one or more clinical AEs during parenteral therapy. During the parenteral therapy period, 26.7% of ertapenem-treated children and 24.0% of ceftriaxone-treated children reported a drug-related clinical and/or laboratory AE (P=0.69). Secondary: The most common drug-related clinical AEs during parenteral therapy were diarrhea, infusion site pain, infusion site erythema and vomiting. Eighteen patients (5.9%) receiving ertapenem and 10 patients (10%) receiving ceftriaxone experienced diarrhea. Fifteen patients (5%) and 1 patient (1%) receiving ertapenem and ceftriaxone, respectively, experienced infusion site pain. Nine patients (3%) receiving ertapenem and 2 patients (2%) receiving ceftriaxone experienced infusion site erythema. Six patients (2%) receiving ertapenem and 2 patients (2%) receiving ceftriaxone experienced vomiting. The most common laboratory AE in both groups was a decrease in the neutrophil count (5.7% in the ertapenem group and 2.2% in the ceftriaxone group). In the ertapenem group, 18.8% of patients experienced more than one symptom at the site of drug administration during parenteral therapy of any intensity. The rates of moderate-to-severe local symptoms were comparable between the treatment groups (5.3% in the ertapenem group and 5.0% in the ceftriaxone group; P=1.000). The most common infusion/injection-related events were local erythema and pain. A total of 4.6% of children in the ertapenem group and 3.0% of children in the ceftriaxone group experienced erythema. A total of 6.6% of children in the ertapenem group and 4.0% of children in the ceftriaxone group experienced administration site pain.
Geddes et al.[48] (1999)	MC, RCT Patients ≥18 years	N=503 Duration of	Primary: Cure rate, clinical and bacteriological	Primary: Clinical response was similar in both groups with 85% in the per-protocol and 68% in the intent-to treat imipenem-cilastatin group compared to 89%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Imipenem-cilastatin 1 g IV TID and the addition of a second antimicrobial such as metronidazole, an aminoglycoside or vancomycin as needed vs levofloxacin 500 mg IV BID, then levofloxacin 500 mg PO and the addition of a second antimicrobial such as metronidazole, an aminoglycoside or vancomycin as needed Patients were switched to PO therapy in the levofloxacin group after 48 hours of IV treatment if signs and symptoms of sepsis had improved.	of age with clinically suspected bacteremia/sepsis	study varied	response within 5 days after completion of antibiotic treatment, clinical response at follow-up 10-30 days after completion of treatment Secondary: Adverse events, duration of hospitalization, mortality	and 77% respectively in the levofloxacin group. Cure rates in the per-protocol and intent-to-treat populations were 69% and 70% respectively for the imipenem-cilastatin group and 84% and 81% respectively for the levofloxacin group 10-30 days post treatment. The bacteriological response rate was similar in both groups with 84% in those treated with imipenem-cilastatin and 87% in the levofloxacin group. Additional antibiotic treatment was required in 31% of patients receiving imipenem-cilastatin and 10% of patients with levofloxacin. Secondary: Safety was evaluated in 499 patients. There was no relevant difference found between each treatment group. The duration of hospitalization was reported for 446 patients. The imipenem-cilastatin group remained hospitalized for 11-11.5 days while there was a 9 day duration of stay for the levofloxacin group (P=0.015). No difference was established in mortality.
Solomkin et al.[46] (1996) Imipenem-cilastatin 500 mg IV QID and placebo infusion	DB, MC, PRO, RCT Patients >18 years of age with signs and symptoms of	N=330 8.6 ± 3.6 days	Primary: Success rate, defined as the lack of any of the following: (1) persistent or	Primary: A clinical success rate of 82% was found in patients receiving imipenem-cilastatin as well as in the ciprofloxacin plus metronidazole IV group (95% CI: -0.074 to 0.067). The success rate in both groups was statistically equivalent. Bacterial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID, then imipenem-cilastatin 500 mg IV QID and placebo PO BID vs ciprofloxacin 400 mg IV BID and metronidazole 500 mg IV QID, then ciprofloxacin 400 mg IV BID and metronidazole 500 mg IV QID and placebo PO BID vs ciprofloxacin 400 mg IV BID and metronidazole 500 mg IV QID, then placebo IV and ciprofloxacin 500 mg PO BID and metronidazole 500mg PO QID Switch to PO intake was made between 3-8 days after starting IV therapy.	intra-abdominal infection, if operative or percutaneous drainage appeared necessary		recurrent infection of the abdomen (2) death related to abdominal infection (3) postsurgical wound infection (4) receiving post-study antibiotic treatment for undocumented intra-abdominal infection Secondary: Efficacy of switching to oral ciprofloxacin and metronidazole compared to continuing IV therapy	eradication or presumed eradication was seen in 88% of the treated population, both in the imipenem-cilastatin IV group and in the ciprofloxacin plus metronidazole IV group (95% CI: -0.050 to 0.108). The overall clinical success rate for imipenem-cilastatin IV was 81%; for ciprofloxacin plus metronidazole IV, it was 84%. Secondary: 47% of valid patients were able to switch to PO therapy. No patients receiving either active antibiotic treatment or placebo therapy died. Of the patients receiving active PO antibiotic treatment, 4% failed compared to 11% of the patients who received imipenem-cilastatin IV then PO placebo, a difference that was not considered statistically significant (P=0.2854). Failure (development of wound infection, abscesses requiring percutaneous drainage or receiving antibiotic treatment post-study without infection) was established in 11% of patients treated with ciprofloxacin and metronidazole IV than PO placebo.
Donahue et al.[47] (1998) Imipenem-cilastatin	DB, DD, MC, PRO Patients ≥18 years of age with	N=414 30 days	Primary: Clinical response (cure, improvement or	Primary: Overall clinical success rate was similar between the two treatment groups (86% of the imipenem-cilastatin group and 88% of the trovafloxacin group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1 g IV TID followed by amoxicillin-clavulanic acid 500 mg PO TID and placebo PO QAM for up to 14 days vs alatrofloxacin 300 mg IV QD and placebo IV BID followed by trovafloxacin 200 mg PO QAM and placebo PO TID for up to 14 days	documented intra-abdominal infections, classified as peritonitis or abscesses, requiring hospitalization for surgical repair or percutaneous drainage		failure as evaluated by intra-abdominal symptoms), bacteriological response (absence or presence of baseline pathogen)	The rate of eradication of frequently isolated baseline pathogens was similar in both groups with 84% of patients treated with imipenem-cilastatin and 82% of those treated with trovafloxacin. Specifically, *Bacteroides fragilis* was isolated in 34 patients in the imipenem-cilastatin treatment group and 82% of these patients were considered to have a successful outcome whereas 97% of patients in the trovafloxacin group were considered clinical successes (P=0.125). Eradication of *Pseudomonas aeruginosa* was reported in 82% of the patients treated with imipenem-cilastatin and 97% in those treated with trovafloxacin.
Chang et al.[25] (1997) Imipenem-cilastatin or meropenem vs combination therapy with one of the following regimens: piperacillin-tazobactam, ciprofloxacin and metronidazole, cefotaxime and metronidazole, aztreonam and	MA Patients with intra-abdominal infections	N=1,227 (10 trials) Variable duration	Primary: Clinical response, defined as cure or improvement of a patient's clinical signs and symptoms (Pain, fever, tenderness, and guarding), with no clinical evidence of infection and no relapse at follow-up	Primary: Eight of the 10 studies showed no significant difference in clinical outcomes between carbapenem monotherapy and combination therapy (P values ranged from 0.064 to 0.440). The overall difference in clinical response rates of -1.6% and a response ratio of 0.99 indicated that there is no statistically significant difference in the outcomes of patients treated with carbapenem monotherapy versus combination therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clindamycin, aminoglycoside and clindamycin, and tobramycin and clindamycin or metronidazole				
Hou et al.[37] (2001) Imipenem-cilastatin 500 mg IV BID (or 1 g IV BID) vs meropenem 500 mg IV BID (or 1 g IV BID)	OL, RCT Hospitalized patients ≥16 years of age with lower respiratory infections, urinary tract infections and other acute infections	N=140 7-14 days	Primary: Cure rate, overall efficacy rate (the proportion of patients cured and markedly improved), clinical efficacy, and adverse events	Primary: The cure rate was 57% in the imipenem-cilastatin group and 66% in the meropenem group (P=0.298). The overall efficacy rate was 87% for the imipenem-cilastatin group and 90% for the meropenem group (P=0.595). The bacterial eradication rates were 86% in both groups. There were 72 cases of adverse drug reactions in the meropenem group and 70 cases in the imipenem-cilastatin group that were evaluated resulting in an adverse drug reaction rate of 9.7% and 8.6%, respectively (P>0.05).
Nelson et al.[34] (2002) Imipenem-cilastatin 20 mg/kg IV QID in addition to cytotoxic chemotherapy and total body irradiation (TBI) vs meropenem 20 mg/kg IV TID in addition to cytotoxic chemotherapy and TBI	RCT Pre-engrafted pediatric bone marrow transplant (BMT) patients	N=32 3-31 days	Primary: Evidence of bacterial infection, need for concurrent antibiotics, incidence of vomiting and duration of concurrent total parenteral nutrition (TPN)	Primary: There was no detectable difference in the evidence of bacterial infection between the two treatment groups. Concurrent antibiotics were required for 7.1 ± 2.0 days in the imipenem-cilastatin group compared to 7.2 ± 1.7 days in the meropenem treatment group (P=0.944). There were 30.38 ± 5.08 episodes of vomiting per course of imipenem-cilastatin, versus 9.75 ± 3.53 episodes per course of meropenem, a difference that was statistically significant (P=0.0021). There was no significant difference in the duration of TPN support required between the imipenem-cilastatin group (19.2 ± 2.9 days) and the meropenem group (13.9 ± 2.4 days; P=0.1662).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Vural et al.[79] (2010) Imipenem-cilastatin 60 mg/kg/day IV in four divided doses vs piperacillin-tazobactam 360 mg/kg/day IV in four divided doses	RCT Patients with acute leukemia, lymphoma and solid tumors who were hospitalized with febrile neutropenia	N=63 (99 episodes) Variable duration	Primary: Success and failure rate	Primary: The overall success rate was 67% and the failure rate was 33% in both treatment groups. The success and failure rates in the piperacillin–tazobactam group were 71% and 29%, respectively. The success and failure rates in the imipenem–cilastatin group were 62% and 38%, respectively (P>0.05 vs piperacillin-tazobactam). There were no deaths in the study and no major adverse effects were seen in either group. Mild adverse effects included nausea, vomiting, transient increase in liver function tests and rash. No patient required discontinuation of the therapy due to adverse effects.
Chen et al.[73] (2010) Imipenem-cilastatin 500-500 mg every 6 hours (IMI/CIL) vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours (TGC)	OL, RCT, MC Patients ≥18 years of age with complicated intra-abdominal infection	N=191 ≤2 weeks	Primary: Clinical response at the test-of-cure (TOC) visit (12-37 days after therapy) for the microbiologically evaluable and microbiologic modified-ITT (m-ITT) populations	Primary: In the microbiologically evaluable population, 86.5% of patients receiving TGC and 97.9% of patients receiving IMI/CIL were cured at the TOC visit (95% CI, -23.05 to 0.7). In the m-ITT population, 81.7% of patients receiving TGC and 90.9% of patients receiving IMI/CIL were cured at the TOC visit (95% CI, -23.4 to 4.9). In the clinically evaluable population, 87.0% of patients receiving TGC and 95.4% of patients receiving IMI/CIL were cured at the TOC visit (95% CI, -18.3 to 1.5). In the clinical m-ITT population (those with complicated appendicitis), 80.4% of patients receiving TGC and 89.8% of patients receiving IMI/CIL were cured at the TOC visit (95% CI, -20.3 to 1.6). The overall incidence of treatment-emergent adverse events was 80.4% for TGC compared to 53.9% for IMI/CIL (P<0.001). Adverse events were primarily gastrointestinal in nature, especially nausea (21.6% vs 3.9%; P<0.001) and vomiting (12.4% vs 2.0%; P=0.005).
Berne et al.[27] (1996)	RCT, DB Patients with	N=129 Duration of IV	Primary: Days of postoperative	Primary: The mean number of days of postoperative fever were significantly less in the meropenem group (3.1) compared to the tobramycin and clindamycin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Meropenem 1 g IV every 8 hours vs tobramycin 5 mg/kg/day divided every 8 hours plus clindamycin 900 mg every 8 hours, both IV	advanced appendicitis	therapy	fever, days of antibiotic therapy, hospital stay	group (4.4, P<0.01). The mean number of days of antibiotic therapy were significantly lower in the meropenem group (6.1) compared to the tobramycin and clindamycin group (7.3, P=0.01). The hospital stay was significantly lower in the meropenem group (8 days) compared to the tobramycin and clindamycin group (9.4, P<0.01).
Klugman et al.[32] (1995) Meropenem 40 mg/kg every 8 hours for 7-14 days vs cefotaxime 75-100 mg/kg every 8 hours for 7-14 days	PRO, RCT Children with a diagnosis of bacterial meningitis	N=190 6 weeks posttreatment	Primary: Clinical response (cure, cure with audiologic sequelae, cure with neurologic sequelae, cure with both audiologic and neurologic sequelae, death), bacteriologic response	Primary: In patients with pre-existing neurologic abnormalities, cure was achieved in 47% of meropenem patients compared to 60% of cefotaxime patients, cure with audiologic sequelae was reported in 6% of meropenem patients and 20% of cefotaxime patients, cure with neurologic sequelae was reported in 35% of meropenem patients and 0% of cefotaxime patients, cure with both audiologic and neurologic sequelae was reported in 12% of meropenem patients and 20% of cefotaxime patients, and death was not reported in any patients in either group. In patients without pre-existing neurological abnormalities, cure was achieved in 79% of meropenem patients compared to 83% of cefotaxime patients, cure with audiologic sequelae was reported in 16% of meropenem patients and 12% of cefotaxime patients, cure with neurologic sequelae was reported in 3% of meropenem patients and 2% of cefotaxime patients, cure with both audiologic and neurologic sequelae was reported in 2% of meropenem patients and 0% of cefotaxime patients, and death was reported in no patients in the meropenem group and 3% of cefotaxime patients. Bacteriologic eradication rates were 100% in both groups.
Odio et al.[33] (1999) Meropenem 40 mg/kg every 8	RCT, PRO, MC Patients 2 months to 12 years of age with a diagnosis of	N=266 5-7 months posttreatment	Primary: Clinical response (cure, survival with mild neurological sequelae, survival	Primary: At the 5-7 week follow-up, no significant differences between the meropenem group and the cefotaxime group were observed with respect to cure, survival with sequelae, or death (P=0.624).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours vs cefotaxime 45 mg/kg every 6 hours Treatment duration for both groups was 7-14 days depending on infection.	bacterial meningitis		with severe neurological sequelae, death), microbiologic efficacy	Severe sequelae were present in 30% of meropenem patients and in 17% of cefotaxime patients, and this difference was not significant (P=0.056). At the 5-7 week visit, severe sequelae in the form of audiology were present in 25% of children in the meropenem group and 15% in the cefotaxime group. By the 5-7 month visit, the percentages had decreased to 18% in the meropenem group and 14% in the cefotaxime group. No significant differences were seen in any group at any time. At the end of treatment, bacterial eradication was observed in 95% of patients in the meropenem group and 96% in the cefotaxime group.
Feurle et al.[69] (2010) Meropenem 1 g 3 times daily for 14 days followed by oral trimethoprim-sulfamethoxazole for 12 months vs ceftriaxone 2 g IV once daily for 14 days followed by oral trimethoprim-sulfamethoxazole for 12 months	RCT, OL Patients with previously untreated Whipple's disease	N=42 Variable duration	Primary: Maintenance of remission	Primary: After 3 months, all patients were in clinical and laboratory remission. After 12 months, the intestinal PAS-positive macrophages of all patients showed evidence of regression from subtype 1 to subtype 3. After a mean follow-up time of 41.5 months, intestinal biopsies in the ceftriaxone group revealed no or only a few scattered PAS-positive macrophages in 17 of 18 patients. The corresponding result in the meropenem group was no or a few PAS-positive macrophages in 17 of 18 patients after a mean follow-up period of evaluation of 39.8 months. The residual macrophages were of type 3, rarely type 4. In all patients, clinical, laboratory, and histopathologic remission was maintained at least up to the time of the last endoscopy, performed approximately 40 months after initial treatment.

Drug regimen abbreviations: BID=twice daily, CI=confidence interval, IM=intramuscular, IV=intravenous, PO=oral, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: DB=double blind, MC=multicenter, OL=open-label, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RR=relative risk, SB=single blind

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Miscellaneous β-Lactam Antibiotics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Aztreonam	inhalation solution, injection	Azactam®*, Azactam-Iso-Osmotic Dextrose®, Cayston®	$$$$$	$$$$$
Cefotetan	injection	N/A	N/A	$$$$-$$$$$
Cefoxitin	injection	Mefoxin®	$$$$$	$$$$-$$$$$
Doripenem	injection	Doribax®	$$$$$	N/A
Ertapenem	injection	Invanz®	$$$$$	N/A
Imipenem and cilastatin	injection	Primaxin®*, Primaxin IM®	$$$$$	$$$$$
Meropenem	injection	Merrem®*	$$$$$	$$$$-$$$$$

*Generic is available in at least one dosage form or strength.
N/A=not available

X. Conclusions

The miscellaneous β-lactam antibiotics are approved to treat a variety of infections, including central nervous system, dermatologic, genitourinary, respiratory, as well as several miscellaneous infections.[1-10] All of the injectable products are available in a generic formulation, with the exception of doripenem and ertapenem.

There are many guidelines that define the appropriate place in therapy for the miscellaneous β-lactam antibiotics. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding

spectrum of activity of the β-lactam. The miscellaneous β-lactam antibiotics are recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, meningitis, skin and soft-tissue infections, pelvic inflammatory disease, infectious exacerbations of COPD, community-acquired pneumonia, nosocomial pneumonia, intra-abdominal infections, febrile neutropenia, and for surgical prophylaxis.[11-12,15-16,19-23,85-87]

Studies have demonstrated comparable efficacy among the miscellaneous β-lactam antibiotics for the treatment of skin and soft-tissue infections, urinary tract infections, endometritis, pneumonia, intra-abdominal infections, and for surgical prophylaxis.[24,30-31,34,37,40,44,49-50,55] Few studies have demonstrated greater efficacy with one agent over another.[41,63] The miscellaneous β-lactam antibiotics have also been shown to be comparable in efficacy to antibacterial agents in other classes.[25-29,32-33,35-36,38-39,42-43,46-48,51-54,56-61,65-68,70-71,73-74,77,79-83] Clinical data from published studies supports similar safety profiles among the miscellaneous β-lactam antibiotics.

Aztreonam inhalation solution is approved to improve respiratory symptoms in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*. Treatment with aztreonam has been associated with improvements in pulmonary function, improved quality of life, and decreased requirement for inhaled or intravenous anti-pseudomonal antibiotics compared to placebo.[76,78,84] An open-label study following patients for 18 months demonstrated continued benefit over time.[75]

There is insufficient evidence to support that one brand miscellaneous β-lactam is safer or more efficacious than another within its given indication. With the exception of aztreonam inhalation solution, the miscellaneous β-lactam antibiotics are only available in an injectable formulation and are primarily administered in the inpatient setting. Since these agents are not indicated as first-line therapy for the management of common infectious diseases that would be seen in general use and due to concerns for the development of resistance, these agents should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous β-lactam antibiotics within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Aztreonam inhalation solution has been shown to improve lung function and reduce exacerbations in cystic fibrosis patients colonized with *P. aeruginosa*.[12] Therefore, these patients should be allowed approval for aztreonam inhalation solution through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand miscellaneous β-lactam antibiotic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2011. Available from Wolters Kluwer Health, Inc. Accessed November 2011.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2011; November 2011.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November 2011.
4. Azactam® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; January 2010.
5. Cayston® [package insert]. Foster City, CA: Gilead Sciences, Inc.; February 2010.
6. Mefoxin® [package insert]. Lake Forest, IL: Bioniche Pharma USA LLC; October 2009.
7. Doribax® [package insert]. Raritan, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc.; October 2010.
8. Ivanz® [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; August 2011.
9. Primaxin® [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; February 2010.
10. Merrem® [package insert]. Wilmington, DE: AstraZeneca; December 2010.
11. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis.2005 Nov 15;41(10):1373-406.
12. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1-110.
13. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 91: Treatment of urinary tract infections in nonpregnant women. Obstet Gynecol 2008;111:785-94.
14. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20.
15. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-S72.
16. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2010. 117 p. Available at: www.goldcopd.com. Accessed October 2011.
17. Braman SS. Chronic cough due to chronic bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129 (1 Suppl): 104S-15S.
18. Braman SS. Chronic cough due to acute bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129 (1 Suppl): 95S-103S.
19. Tunkel AR, Hartman BJ, Kaplan SL, et al. Infectious Diseases Society of America. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267-84.
20. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. Circulation. Jun 2005;111:e394-e434.
21. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50:133-64.
22. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis. 2004;38:1706–15.
23. American Thoracic Society and the Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388–416.
24. MacGregor RR, Graziani AL, Samuels P. Randomized, double-blind study of cefotetan and cefoxitin in the post-cesarean section endometritis. Am J Obstet Gynecol. 1992 Jul;167(1):139-43.
25. Chang DC, Wilson SE. Meta-analysis of the clinical outcomes of carbapenem monotherapy in adjunctive treatment of intra-abdominal infections. Am J Surg. 1997; 174:284-90.

26. Kow L, Toouli J, Brookman J, McDonald PJ. Comparison of cefotaxime plus metronidazole versus cefoxitin for prevention of wound infection after abdominal surgery. World J Surg. 1995;19:680-6.
27. Berne TV, Yellin AE, Appleman MD, Heseltine PN, Gill MA. Meropenem versus tobramycin with clindamycin in the antibiotic management of patients with advanced appendicitis. J Am Coll Surg. 1996 May;182(5):403-7.
28. Bjornson HS, Ramirez-Ronda C, Saavedra S, River-Vazquez CR, Liu C, Hinthorn DR. Comparison of empiric aztreonam and aminoglycoside regimens in the treatment of serious gram-negative lower respiratory infections. Clin Ther. 1993 Jan-Feb;15(1):65-78.
29. Friedland IR, McCarroll KA, DiNubile MJ, Woods GL. Ertapenem as initial antimicrobial monotherapy for patients with chronic obstructive pulmonary disease hospitalized with typical community-acquired pneumonia. Pulm Pharmacol Ther. 2004;17:199-203.
30. Romanelli G, Cravarezza P, Pozzi A, et al. Carbapenems in the treatment of severe community-acquired pneumonia in hospitalized elderly patients: a comparative study against standard therapy. J Chemother. 2002 Dec;14(6):609-17.
31. Bartoloni A, Strohmeyer M, Corti G, et al. Multicenter randomized trial comparing meropenem (1.5g daily) and imipenem/cilastatin (2g daily) in the hospital treatment of community-acquired pneumonia. Drugs Exp Clin Res. 1999;25(6):243-52.
32. Klugman KP, Dagan R; The Meropenem Meningitis Study Group. Randomized comparison of meropenem with cefotaxime for treatment of bacterial meningitis. Antimicrob Agents Chemother 1995;39):1140-6.
33. Odio CM, Puig JR, Feris JM, Khan WN, Rodriguez WJ, McCracken GH, et al. Prospective, randomized, investigator-blinded study of efficacy and safety of meropenem vs cefotaxime therapy in bacterial meningitis in children. Pediatr Infect Dis J. 1999 Jul;18(7):581-90.
34. Nelson WK, Rayback PA, Quinones R, et al. Empiric carbapenem monotherapy in pediatric bone marrow transplant recipients. Ann Pharmacother. 2002 Sep;36(9):1360-5.
35. Paul M, Yahav D, Fraser A, Leibovici L. Empirical antibiotic monotherapy for febrile neutropenia: systemic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2006;57:176-89.
36. Gesser RM, McCarroll K, Teppler H, Woods GL. Efficacy of ertapenem in the treatment of serious infections caused by enterobacteriaceae: analysis of pooled clinical trial data. J Antimicrob Chemother. 2003;51:1253-60.
37. Hou F, Wu G, Zheng B. A randomized, controlled clinical trial of meropenem and imipenem/cilastatin in the treatment of acute bacterial infections. Zhonghua Nei Ke Za Zhi.2001 Sep;40(9):589-93.
38. Gesser RM, McCarroll KA, Woods GL. Evaluation of outpatient treatment with ertapenem in a double blind controlled clinical trial of complicated skin/skin structure infections. J Infect. 2004;48:32-8.
39. Lipsky BA, Armstrong DG, Citron DM, Tice AD, Morgenstern DE, Abramson MA. Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomized, controlled, double-blinded, multicentre trial. Lancet. 2005 Nov 12;366:1695-703.
40. Nichols RL, Smith JW. Meropenem versus imipenem/cilastatin in the treatment of hospitalized patients with skin and soft tissue infections. South Med J. 1995 Apr;88(4):337-44.
41. Itani K, Wilson S, Awad S, et al. Ertapenem versus cefotetan prophylaxis in elective colorectal surgery. N Engl J Med 2006;355:2640-51.
42. Friman O, Cars O, Back E, Beckman H, Carlsson M, Forssell J, et al. Randomized comparison of aztreonam and cefuroxime in gram-negative upper urinary tract infections. Infection. 1989;17(5):284-9.
43. Wells WG, Woods GL, Jiang Q, Gesser RM; The Protocol 014 and 021 Study Groups. Journal of Antimicrobial Chemotherapy. 2004;53 Suppl S2:ii67-ii74.
44. Cox CE, Holloway WJ, Geckler RW. A multicenter comparative study of meropenem and imipenem/cilastatin in the treatment of complicated urinary tract infections in hospitalized patients. Clin Infect Dis. 1995;21:86-92.
45. Ryo E, Ikeya M, Sugimoto M. Clinical study of the effectiveness of imipenem/cilastatin sodium as the antibiotics of first choice in the expectant management of patients with preterm premature rupture of membranes. J Infect Chemother. 2005;11:32-6.
46. Solomkin JS, Reinhart HH, Dellinger EP, Bohnen JM, Rotstein OD, Vogel SB, et al. Results of randomized trial comparing sequential intravenous/oral treatment with ciprofloxacin plus metronidazole to imipenem/cilastin for intra-abdominal infections. Ann Surg. 1996;223(3):303-15.
47. Donahue PE, Smith DL, Yellin AE, Mintz SJ, Bur F, Luke DR; The Trovafloxacin Surgical Group. Trovafloxacin in the treatment of intra-abdominal infections: results of a double-blind, multicenter comparison with imipenem/cilastatin. Am J Surg. 1998 Dec;176 Suppl 6A:53S-61S.

48. Geddes A, Thaler M, Schonwald S, Harkonen M, Jacobs F, Nowotny I. Levofloxacin in the empirical treatment of patients with suspected bacteraemia/sepsis: comparison with imipenem/cilastatin in an open, randomized trial. J Antimicrob Chemother. 1999;44:799-810.
49. Fabian T, File T, Embil J, et al. Meropenem versus imipenem-cilastatin for the treatment of hospitalized patients with complicated skin and skin structure infections: results of a multicenter, randomized, double-blind comparative study. Surg Infect (Larchmt) 2005;6:269-82.
50. Chastre J, Wunderink R, Prokocimer P, et al. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. Crit Care Med 2008;36:1089-96.
51. Réa-Neto A, Niederman M, Lobo S, et al. Efficacy and safety of doripenem versus piperacillin/tazobactam in nosocomial pneumonia: a randomized, open-label, multicenter study. Curr Med Res Opin 2008;24:2113-26.
52. Yanagihara K, Fukuda Y, Seki M, et al. Clinical comparative study of sulbactam/ampicillin and imipenem/cilastatin in elderly patients with community-acquired pneumonia. Intern Med 2006;45:995-9.
53. Schmitt D, Leitner E, Welte T, et al. Piperacillin/tazobactam vs imipenem/cilastatin in the treatment of nosocomial pneumonia--a double blind prospective multicentre study. Infection 2006;34:127-34.
54. Joshi M, Metzler M, McCarthy M, et al. Comparison of piperacillin/tazobactam and imipenem/cilastatin, both in combination with tobramycin, administered every 6 h for treatment of nosocomial pneumonia. Respir Med 2006;100:1554-65.
55. Lucasti C, Jasovich A, Umeh O, et al. Efficacy and tolerability of IV doripenem versus meropenem in adults with complicated intra-abdominal infection: a phase III, prospective, multicenter, randomized, double-blind, noninferiority study. Clin Ther 2008;30:868-83.
56. Namias N, Solomkin J, Jensen E, et al. Randomized, multicenter, double-blind study of efficacy, safety, and tolerability of intravenous ertapenem versus piperacillin/tazobactam in treatment of complicated intra-abdominal infections in hospitalized adults. Surg Infect (Larchmt) 2007;8:15-28.
57. Yellin A, Johnson J, Higareda I, et al. Ertapenem or ticarcillin/clavulanate for the treatment of intra-abdominal infections or acute pelvic infections in pediatric patients. Am J Surg 2007;194:367-74.
58. Falagas M, Peppas G, Makris G, et al. Meta-analysis: ertapenem for complicated intra-abdominal infections. Aliment Pharmacol Ther 2008;27:919-31.
59. Milsom J, Smith D, Corman M, et al. Double-blind comparison of single-dose alatrofloxacin and cefotetan as prophylaxis of infection following elective colorectal surgery. Trovafloxacin Surgical Group. Am J Surg 1998;176(6A Suppl):46S-52S.
60. Noyes N, Berkeley A, Freedman K, et al. Incidence of postpartum endomyometritis following single-dose antibiotic prophylaxis with either ampicillin/sulbactam, cefazolin, or cefotetan in high-risk cesarean section patients. Infect Dis Obstet Gynecol 1998;6:220-3.
61. Bracero L. Ampicillin/sulbactam versus cefotetan for the prevention of infection following cesarean delivery in high-risk patients: a randomized double-blind trial. Gynecol Obstet Invest 1997;44:21-5.
62. Hemsell D, Johnson E, Hemsell P, et al. Cefazolin is inferior to cefotetan as single-dose prophylaxis for women undergoing elective total abdominal hysterectomy. Clin Infect Dis 1995;20:677-84.
63. Liberman M, Greason K, Frame S, et al. Single-dose cefotetan or cefoxitin versus multiple-dose cefoxitin as prophylaxis in patients undergoing appendectomy for acute nonperforated appendicitis. J Am Coll Surg 1995;180:77-80.
64. Arguedas A, Cespedes J, Botet F, et al. Safety and tolerability of ertapenem versus ceftriaxone in a double-blind study performed in children with complicated urinary tract infection, community-acquired pneumonia or skin and soft-tissue infection. Int J Antimicrob Agents 2009;33:163-7.
65. Roy S, Hemsell, D, Gordon S, Godwin D, Pearlman M, Luke D; The Trovafloxacin Surgical Group. Oral trovafloxacin compared with intravenous cefoxitin in the prevention of bacterial infection after elective vaginal or abdominal hysterectomy for nonmalignant disease. Am J Surg. 1998;176 Suppl 6A:62S-6S.
66. McGregor JA, Crombleholme WR, Newton E, Sweet RL, Tuomala R, Gibbs RS. Randomized comparison of ampicillin-sulbactam to cefoxitin and doxycycline or clindamycin and gentamicin in the treatment of pelvic inflammatory disease or endometritis. Obstet Gynecol. 1994 Jun;83(6):998-1004.
67. Corey GR, Wilcox MH, Talbot GH, et al. CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65 Suppl 4:iv41-51.
68. Wilcox MH, Corey GR, Talbot GH, et al. CANVAS 2: the second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65 Suppl 4:iv53-iv65.

69. Feurle GE, Junga NS, Marth T. Efficacy of ceftriaxone or meropenem as initial therapies in Whipple's disease. Gastroenterology 2010;138:478-86.
70. Corey GR, Wilcox M, Talbot GH, et al. Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. Clin Infect Dis 2010;51:641-50.
71. Freire AT, Melnyk V, Kim MJ, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. Diagn Microbiol Infect Dis 2010;68:140-51.
72. Chuang YC, Chang CM, Aradhya S, et al. Efficacy and safety of tigecycline monotherapy compared with vancomycin-aztreonam in the treatment of complicated skin and skin structure infections in patients from India and Taiwan. J Microbiol Immunol Infect 2011;44:116-24.
73. Chen Z, Wu J, Zhang Y, et al. Efficacy and safety of tigecycline monotherapy vs imipenem/cilastatin in Chinese patients with complicated intra-abdominal infections: a randomized controlled trial. BMC Infect Dis 2010;10:217.
74. Kobayashi R, Sato T, Nakajima M, et al. Piperacillin/tazobactam plus ceftazidime versus sulbactam/ampicillin plus aztreonam as empirical therapy for fever in severely neutropenic pediatric patients. J Pediatr Hematol Oncol 2009;31:270-3.
75. Oermann CM, Retsch-Bogart GZ, Quittner AL, et al. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. Pediatr Pulmonol 2010;45:1121-34.
76. Wainwright CE, Quittner AL, Geller DE, et al. Aztreonam for inhalation solution (AZLI) in patients with cystic fibrosis, mild lung impairment, and P. aeruginosa. J Cyst Fibros 2011;10:234-42.
77. Jeong WK, Park JW, Lim SB, et al. Cefotetan versus conventional triple antibiotic prophylaxis in elective colorectal cancer surgery. J Korean Med Sci 2010;25:429-34.
78. Retsch-Bogart GZ, Quittner AL, Gibson RL, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. Chest 2009;135:1223-32.
79. Vural S, Erdem E, Gulec SG, et al. Imipenem-cilastatin versus piperacillin-tazobactam as monotherapy in febrile neutropenia. Pediatr Int 2010;52:262-7.
80. Naber KG, Llorens L, Kaniga K, et al. Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for treatment of complicated lower urinary tract infection and pyelonephritis. Antimicrob Agents Chemother 2009;53:3782-92.
81. Saltoglu N, Dalkiran A, Tetiker T, et al. Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital. Clin Microbiol Infect 2010;16:1252-7.
82. Redman R, Damiao R, Kotey P, et al. Safety and efficacy of intravenous doripenem for the treatment of complicated urinary tract infections and pyelonephritis. J Chemother 2010;22:384-91.
83. Ito I, Kadowaki S, Tanabe N, et al. Tazobactam/piperacillin for moderate-to-severe pneumonia in patients with risk for aspiration: comparison with imipenem/cilastatin. Pulm Pharmacol Ther 2010;23:403-10.
84. McCoy KS, Quittner AL, Oermann CM, et al. Inhaled aztreonam lysine is effective in intensively-treated patients with cystic fibrosis. Am J Respir Crit Care Med 2008;178:921–928.
85. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, LeFrock JL, Lew DP, Mader JT, Norden C, Tan JS; Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004 Oct 1;39(7):885-910.
86. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR, Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:e56-93.
87. Chaudhuri A, Martinez-Martin P, Kennedy PG, Andrew Seaton R, Portegies P, Bojar M, Steiner I; EFNS Task Force. EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. Eur J Neurol 2008;15:649-59.
88. Flume P, O'Sullivan B, Robinson K, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2007;176:957-969.
89. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011;53:e25-76.
90. Ramsdell J, Narsavage GL, Fink JB; American College of Chest Physicians' Home Care Network Working Group. Management of community-acquired pneumonia in the home: an American College of Chest Physicians clinical position statement. Chest 2005;127:1752-63.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Chloramphenicol
AHFS Class 081208
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I. Overview

Chloramphenicol is approved for the treatment of serious infections caused by susceptible microorganisms, acute infections caused by *Salmonella typhi*, and as part of a cystic fibrosis regimen.[1-3] However, it should only be used when less potentially dangerous drugs are ineffective or contraindicated. Chloramphenicol exhibits its antibacterial effect by interfering with the ribosomal transfer of activated amino acids from ribonucleic acid and thus inhibiting bacterial protein synthesis.[3]

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) have occurred following treatment with chloramphenicol.[1-3] There have also been reports of aplastic anemia progressing to leukemia that were attributed to chloramphenicol. Blood dyscrasias have occurred after both short- and long-term therapy.

The chloramphenicol products that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Chloramphenicol is available in a generic formulation. This class was last reviewed in August 2009.

Table 1. Chloramphenicol Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Chloramphenicol	injection	N/A	chloramphenicol

PDL=Preferred Drug List
N/A=Not available

Chloramphenicol has been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the FDA-approved indications for chloramphenicol that are noted in Table 4. This agent may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since its safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to Chloramphenicol[1-3]

Organism	Chloramphenicol
Gram-Negative Aerobes	
Haemophilus influenzae	✔
Rickettsia	✔
Salmonella species, including *Salmonella typhi*	✔
Miscellaneous Organisms	
Lymphogranuloma-psittacosis group	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of chloramphenicol are summarized in Table 3.

Table 3. Treatment Guidelines Using Chloramphenicol

Clinical Guideline	Recommendation(s)
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines: Management of Encephalitis[4] (2008)**	Specific Therapy – Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or trimethoprim-sulfamethoxazole is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; trimethoprim-sulfamethoxazole is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either trimethoprim-sulfamethoxazole or cefixime, is recommended. Specific Therapy - *Rickettsioses and Ehrlichioses* • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended.

European Federation of Neurological Societies (EFNS): **Guideline on the Management of Community-acquired Bacterial Meningitis[5] (2008)**	Empirical Therapy
	• Ceftriaxone 2 g every 12–24 hours or cefotaxime 2 g every 6–8 hours.
	• Alternative therapy: Meropenem 2 g every 8 hours or chloramphenicol 1 g every 6 hours.
	• If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg.
	• Ampicillin/Amoxicillin 2 g every 4 hours if *Listeria* is suspected.
	Pathogen Specific Therapy
	• Penicillin-sensitive pneumococcal meningitis:
	  o Benzyl penicillin 250,000 U/kg/day, ampicillin/amoxicillin 2 g every 4 hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every 6–8 hours
	  o Alternative therapy: meropenem 2 g every 8 hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily
	• Pneumococcus with reduced susceptibility to penicillin or cephalosporins:
	  o Ceftriaxone or cefotaxime plus vancomycin ± rifampicin
	  o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin
	• Meningococcal meningitis:
	  o Benzyl penicillin, ceftriaxone, or cefotaxime
	  o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin
	• *Haemophilus influenzae* type B:
	  o Ceftriaxone or cefotaxime
	  o Alternative therapy: chloramphenicol–ampicillin/amoxicillin
	• Listerial meningitis:

Clinical Guideline	Recommendation(s)
	o Ampicillin or amoxicillin 2 g every 4 hours ± gentamicin 1–2 mg every 8 hours for the first 7– 10 days o Alternative therapy: trimethoprim–sulfamethoxazole 10–20 mg/kg every 6–12 hours or meropenem • *Staphylococcal* species: o Flucloxacillin 2 g every 4 hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem • Pseudomonal meningitis: o Meropenem ± gentamicin
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Bacterial Meningitis[6] (2004)**	• Third-generation cephalosporins are the drugs of choice for the empirical therapy of patients with *H. influenzae* type b meningitis due to the emergence of resistance to chloramphenicol. • In clinical trials, the third-generation cephalosporins have been found to be more efficacious than chloramphenicol and cefuroxime and are recommended for the treatment of childhood bacterial meningitis. • Chloramphenicol may be used as an alternative therapy for the treatment of bacterial meningitis caused by *H. influenzae*, *N. meningitides*, and *S. pneumoniae*.
Working Group on Civilian Biodefense (WGCB): **Plague as a Biological Weapon: Medical and Public Health Management Consensus Statement[22] (2000)**	• For adults with pneumonic plague in the contained casualty settings, the preferred choice is streptomycin or gentamicin and alternative choices include doxycycline, ciprofloxacin, or chloramphenicol. • For children with pneumonic plague in the contained casualty settings, the preferred choice is streptomycin or gentamicin and alternative choices include doxycycline, ciprofloxacin, or chloramphenicol. • For pregnant women with pneumonic plague in the contained casualty settings, the preferred choice is gentamicin and an alternative choice is doxycycline. • For adults with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline, or ciprofloxacin and the alternative choice is chloramphenicol. • For children with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin and an alternative choice is chloramphenicol. • For pregnant women with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin and an alternative choice is chloramphenicol.
Centers for Disease Control and Prevention (CDC): **Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichioses, and Anaplasmosis—United States[7] (2006)**	• The CDC recommends doxycycline as the treatment of choice for all tickborne rickettsial diseases in children and adults. • Chloramphenicol is an alternative drug that has been used to treat Rocky Mountain spotted fever (RMSF); however, it is associated with various side effects and might require monitoring of blood indices. • Epidemiologic studies in which CDC case report data have been used suggested that patients with RMSF treated with chloramphenicol have a higher risk of dying than persons who received a tetracycline.

III. Indications

The Food and Drug Administration (FDA)-approved indications for chloramphenicol are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for Chloramphenicol[1-3]

Indications	Chloramphenicol
Serious infections caused by susceptible strains, including *Salmonella* species, *H. influenzae*, *Rickettsia*, Lymphogranuloma-psittacosis group, gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections, and susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents	✔
Acute infections caused by *Salmonella typhi*	✔
Cystic fibrosis regimens	✔

IV. Pharmacokinetics

The pharmacokinetic parameters for chloramphenicol are listed in Table 5.

Table 5. Pharmacokinetic Parameters for Chloramphenicol[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Chloramphenicol	Not reported	50-80	Liver (90)	Renal (5-15) Feces (2-4)	1.6-3.3

V. Drug Interactions

Significant drug interactions with chloramphenicol are listed in Table 6.

Table 6. Significant Drug Interactions with Chloramphenicol[4]

Generic Name(s)	Significance Level	Interaction	Mechanism
Chloramphenicol	1	Anticoagulants	The hypoprothrombinemic effect of anticoagulants may be increased by chloramphenicol and bleeding may occur.
Chloramphenicol	1	Vaccines, live	Chloramphenicol may decrease the effectiveness of live vaccines when the two are co-administered.
Chloramphenicol	2	Hydantoins	Concurrent use may result in an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, and tremor).
Chloramphenicol	2	Sulfonylureas	Concurrent use may result in hypoglycemia (central nervous system depression, seizures).

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with chloramphenicol are listed in Table 7. The boxed warning for chloramphenicol is listed in Table 8.

Table 7. Adverse Drug Events (%) Reported with Chloramphenicol[1-3]

Adverse Events	Chloramphenicol
Central Nervous System	
Confusion	✔
Delirium	✔
Depression	✔
Fever	✔
Headache	✔
Optic neuritis	✔
Peripheral neuritis	✔
Gastrointestinal	
Diarrhea	✔
Enterocolitis	✔
Glossitis	✔
Nausea	✔
Stomatitis	✔
Vomiting	✔
Hematologic	
Aplastic anemia	✔
Granulocytopenia	✔
Hemolytic anemia	✔
Hypoplastic anemia	✔
Leukemia	✔
Leukopenia	✔
Neutropenia	✔
Pancytopenia	✔
Thrombocytopenia	✔
Other	
Anaphylaxis	✔
Angioedema	✔
Hypersensitivity reactions	✔
Gray Syndrome	✔

✔ Percent not specified

Table 8. Boxed Warning for Chloramphenicol[1]

WARNING
Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in Indications. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections. It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

VII. Dosing and Administration

The usual dosing regimens for chloramphenicol are listed in Table 9.

Table 9. Usual Dosing Regimens for Chloramphenicol[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Chloramphenicol	Unspecified Infections: 50 mg/kg/day IV in divided doses every 6 hours. Patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible.	Unspecified Infections: Infants and children: 50 mg/kg/day in divided doses every 6 hours. Severe infections may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Neonates: 25 mg/kg/day in divided doses every 6 hours. After the first 2 full weeks of life, 50 mg/kg/day in divided doses every 6 hours may be administered.	Injection: 1 g

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of chloramphenicol are summarized in Table 10.

Table 10. Comparative Clinical Trials with Chloramphenicol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bacterial Meningitis				
Shann et al.[9] (1985) Chloramphenicol 25 mg/kg IM every 6 hours vs chloramphenicol 25 mg/kg IV every 6 hours plus penicillin Once clinical improvement was observed patients received oral chloramphenicol palmitate 25 mg/kg every 6 hours for a total of 14 days.	RCT, PRO, MC Children with bacterial meningitis	N=367 14 days	Primary: Cumulative endpoint of mortality, brain damage, and persistent illness; death	Primary: The cumulative outcome measure was poor (death, discharged with brain damage) in 38% of the patients receiving chloramphenicol alone compared to 40% of those receiving combination therapy. There was no significant difference in mortality between the chloramphenicol and the combination treatment groups (26% vs 27%).
Nathan et al.[11] (2005) Chloramphenicol 100 mg/kg IM as a single dose vs	RCT, OL, MC Patients >2 months of age with meningitis	N=510 1 month	Primary: Treatment failure at 72 hours Secondary: Mortality within 72 hours, clinical sequelae at 72 hours, clinical	Primary: Both treatment groups exhibited a treatment failure rate of 9% (90% CI: -3.8 to 4.5). Secondary: There was no significant difference in the mortality rate at 72 hours between the chloramphenicol and ceftriaxone groups (5% vs 6%, respectively; 90% CI: -2.3 to 3.8).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ceftriaxone 100 mg/kg IM as a single dose			failure between 24 and 48 hours requiring a second injection	Clinical failure took place in 4% of the chloramphenicol-group survivors and 3% of the ceftriaxone-treated patients (90% CI: -3.3 to 2.8). There was no significant difference in the re-injection rate between the chloramphenicol and ceftriaxone groups (8% vs 7%, respectively; 90% CI: -4.7 to 3.0). Neurologic sequelae occurred in 5% of patients on chloramphenicol and 7% of patients on ceftriaxone therapy (90% CI: -2.1 to 5.1).
Peltola et al.[16] (1989) Chloramphenicol 100 mg/kg/day in 4 divided doses vs ampicillin 250 mg/kg/day in 4 divided doses plus chloramphenicol (administered until bacterial strain was shown to be susceptible to ampicillin alone) vs cefotaxime 150 mg/kg/day in 4 divided doses vs ceftriaxone 100	RCT, MC Children 3 months to 15 years of age with bacterial meningitis	N=220 7 days	Primary: CSF culture pathogens, time to sterile CSF culture	Primary: The CSF became sterile significantly earlier in meningococcal meningitis compared to patients presenting with *H influenzae* type b (P<0.01). At 24 hours, positive cultures were found only in patients receiving chloramphenicol. At 24 hours, the CSF was sterile in a greater proportion of patients treated with cephalosporins compared to those treated with ampicillin-chloramphenicol or chloramphenicol (P<0.05). On day 4, CSF culture was positive in only one patient, who was treated with chloramphenicol.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg once daily				
Rodriguez et al.[10] (1986) Chloramphenicol 100 mg/kg/day IV in 4 divided doses plus ampicillin 400 mg/kg/day IV in 4-6 divided doses vs ampicillin 400 mg/kg/day IV in 4-6 divided doses plus sulbactam 50 mg/kg/day	RCT, PRO, MC Hospitalized patients 1 month to 14 years of age with meningitis	N=81 10 days	Primary: Mortality rate, resolution of symptoms, complications, adverse effects	Primary: Of the patients with assessable CSF pathogens, the mortality rate was 3% in the ampicillin-sulbactam group and 18% in the chloramphenicol-ampicillin group. Neurologic sequelae occurred in 12% of patients on ampicillin-sulbactam and 18% of patients on chloramphenicol-ampicillin therapy. The mean time to resolution of symptoms was 4.4 days in the ampicillin-sulbactam group and 4.8 days in the chloramphenicol-ampicillin. Abnormal laboratory findings were found in 20% of the ampicillin-sulbactam group and 35% in the chloramphenicol-ampicillin group.
Girgis et al.[12] (1988) Chloramphenicol 100 mg/kg/day plus ampicillin 160 mg/kg/day every 6 hours (AMCL) vs ceftriaxone 100 mg/kg once daily	RCT Patients with bacterial meningitis	N=100 6 days	Primary: CSF leukocyte count, glucose, protein content, disappearance of meningeal irritation, fever defervescence, patient alertness, mortality rate	Primary: There was no significant difference between the two groups in the disappearance of meningeal irritation, fever defervescence, and patient alertness. There was no significant difference between the two groups in the CSF leukocyte count, glucose or protein content at baseline, as well as the final evaluation. There was no significant difference between the two groups in mortality. While 20% of patients treated with AMCL died, the mortality in the ceftriaxone group was 7%.
Girgis et al.[19] (1987) Chloramphenicol 100 mg/kg/day IV plus ampicillin 160	RCT Patients 16 to 30 years of age with bacterial meningitis	N=30 6 days	Primary: Mortality, time taken for defervescence, time for patients to regain full	Primary: One patient in each group died within 24 hours of initiation of therapy. Both had meningitis due to *S. pneumoniae*. The mean number of days to become afebrile were 3.4 and 3.5 for group 1 and group 2, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/day IV every 6 hours (group 1) vs ceftriaxone 100 mg/kg IV once daily (group 2)			consciousness	The mean number of days to regain full consciousness was 3.9 and 2.5 for group 1 and group 2, respectively.
Jacobs et al.[13] (1985) Chloramphenicol 25 mg/kg/dose IV plus ampicillin 50-100 mg/kg/dose IV every 6 hours vs cefotaxime 50 mg/kg/dose IV every 6 hours	RCT, PRO Patients 1 week to 16 years of age with meningitis	N=50 3 months	Primary: Clinical cure rate, survival without sequelae, duration of therapy	Primary: There was no significant difference in the clinical cure rate between the chloramphenicol-ampicillin and cefotaxime groups (96% vs 100%, respectively; P>0.5). There was no significant difference in survival without detectable sequelae between the chloramphenicol-ampicillin and cefotaxime groups (77% vs 78%, respectively). Mean duration of therapy was similar in the chloramphenicol-ampicillin and cefotaxime groups (11.9 and 11.1 days, respectively).
Rodriguez et al.[14] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in 4 divided doses plus ampicillin 400 mg/kg/day IV in 6 divided doses vs ceftazidime 150 mg/kg/day IV	RCT, OL Patients 1 month to 15 years of age with meningitis	N=100 Up to 6 months	Primary: Clinical cure rate, clinical improvement, mortality rate, neurological sequelae, mean duration of therapy	Primary: After the first 24 hours of therapy, 10% of the patients died, 2% clinically improved, and 88% were cured in the ceftazidime group. In the chloramphenicol-ampicillin group, 10% of patients died, 1% clinically improved, and 81% were cured in the ceftazidime. Seizures occurred in 54% of patients treated with ceftazidime and 51% of patients treated with chloramphenicol-ampicillin therapy. Mean duration of therapy was 10.2 and 10.4 days in the ceftazidime and chloramphenicol-ampicillin groups, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
divided into 3 doses, administered every 8 hours				
Marks et al.[15] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in 4 divided doses plus ampicillin 300-400 mg/kg/day IV every 6 hours vs cefuroxime 225 mg/kg/day IV divided into 3 doses, administered every 8 hours	RCT, MC Patients 3 months to 16 years of age with bacterial meningitis	N=107 Up to 6 months	Primary: Clinical cure rate, CSF sterilization rate	Primary: Clinical cure rate was 95% in both treatment groups. There was no significant difference in the CSF sterilization rates between the cefuroxime and chloramphenicol-ampicillin groups (90% vs 100%, respectively).
Johansson et al.[20] (1982) Chloramphenicol and ampicillin IV every 6 hours for at least 5 days (A+C) vs cefuroxime IV every 8 hours for at least 5 days (CXM)	RCT, MC Patients with bacterial meningitis	N=67 ≥5 days	Primary: Efficacy and safety	Primary: Complete resolution of symptoms was recorded in 18 of the 21 patients in the CXM group and in 14 of the 19 patients in the A+C group. Two patients died in each group. Adverse events were reported on eight occasions in 7 patients in the CXM group and in 4 patients in the A + C group. Rashes developed in 2 CXM patients and 3 A + C patients. Fever was noted in 2 CXM patients. Moderately severe diarrhea which required symptomatic treatment developed in 1 patient in each group, and 1 CXM patient had repeated thrombophlebitis.
Typhoid and Enteric Fever				
Tanaka-Kido et al.[17]	RCT	N=36	Primary: Clinical cure rate,	Primary: There was no significant difference between the chloramphenicol and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1990) Chloramphenicol 100 mg/kg/day in 4 divided doses, which was continued for 8 days after the last fever day vs aztreonam 150 mg/kg/day IV in 3 divided doses, which was continued for 8 days after the last fever day	Patients 2-6 years of age with typhoid fever	1 month	fever duration, relapse rate, adverse effects	aztreonam groups in clinical cure rate (94% vs 100%). There was no significant difference between the chloramphenicol and aztreonam groups in fever duration (4.1 days vs 5.9 days, respectively; P>0.05). There were no relapses in either of the two groups. While there was no incidence of anemia in the aztreonam group, there were 5 cases of anemia in the chloramphenicol group (P<0.05). There was no difference in the incidence of leukopenia and neutropenia between the two treatment groups (P>0.05). The approximate mean duration of antibiotic therapy was 15 days in the aztreonam group and 13 days in the chloramphenicol group.
Gotuzzo et al.[18] (1994) Chloramphenicol 50 mg/kg/day PO/IV in 4 divided doses for 14 days vs aztreonam 2 g IV every 8 hours for 10 days	RCT, MC Patients >14 years of age with typhoid fever	N=44 10 weeks	Primary: Clinical cure rate, fever duration, bacteremia	Primary: There was a significant difference between the chloramphenicol and aztreonam groups in terms of clinical cure rates (100% vs 68%, respectively; P<0.01). Defervescence occurred more quickly in patients receiving chloramphenicol compared to patients on aztreonam therapy (4.5 days vs 6.6 days, respectively; P<0.03). There were no relapses in either of the two groups. While 24-hour positive blood cultures occurred in 32% of patients on chloramphenicol therapy, none of the patients in the aztreonam group had positive blood cultures (P<0.05). Adverse reactions experienced by patients in each treatment group deemed unusual or mild with no statistical difference found between the two groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Arjyal et al.[21] (2011) Chloramphenicol 75 mg/kg/day in four divided doses for 14 days vs gatifloxacin 10 mg/kg once daily for 7 days	RCT, OL Patients with uncomplicated enteric fever	N=853 6 months	Primary: Treatment failure Secondary: Fever clearance time, late relapse, and fecal carriage	Primary: There were 14 treatment failures in the chloramphenicol group and 12 treatment failures in the gatifloxacin group (HR 0.86; 95% CI, 0.40 to 1.86; P=0.70). Secondary: The median time to fever clearance was 3.95 days in the chloramphenicol group and 3.90 in the gatifloxacin group (P=0.64). There was no significant difference between the treatment groups in relapses until day 31 (P=0.35) or day 62 (P=0.77). Only three of 148 patients receiving chloramphenicol and none of 154 patients receiving gatifloxacin were stool-culture-positive at the end of 1 month (P=0.12). At the end of 3 months, only one patient in the chloramphenicol group had a positive stool culture, and at 6 months no patients had a positive stool culture. In the chloramphenicol group, 25% of culture-positive patients experienced at least one adverse event. In the gatifloxacin group, 16.9% of culture-positive patients experienced at least one adverse event.

Drug regimen abbreviations: IM=intramuscular, IV=intravenous, PO=oral
Study abbreviations: CI=confidence interval, CSF=cerebrospinal fluid, MC=multicenter OL=open-label, PRO=prospective, RCT=randomized trial

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 11. Relative Cost of Chloramphenicol

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Chloramphenicol	injection	N/A	N/A	$$$$

N/A=Not available

X. Conclusions

Chloramphenicol is approved for the treatment of serious infections caused by susceptible microorganisms, acute infections caused by *Salmonella typhi*, and as part of a cystic fibrosis regimen.[1-3] It is available in a generic formulation.

Guidelines recommend chloramphenicol as an alternative treatment option in patients with bacterial meningitis and Rocky Mountain spotted fever.[4-7] Clinical trials have demonstrated similar efficacy with chloramphenicol (as monotherapy or in combination with ampicillin) compared to broad-spectrum cephalosporins in patients with bacterial meningitis.[11-15,19-20]

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after both short-term and prolonged therapy with chloramphenicol. It should only be used when less potentially dangerous drugs are ineffective or contraindicated.[1-3] To facilitate appropriate studies and observation during therapy, it is desirable that patients receiving chloramphenicol be hospitalized.

Therefore, all brand chloramphenicol products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand chloramphenicol product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2011. Available from Wolters Kluwer Health, Inc. Accessed October 2011.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2011; October 2011.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed October 2011.
4. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM, Whitley RJ, Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303-27.
5. Chaudhuri A, Martinez-Martin P, Kennedy PG, Andrew Seaton R, Portegies P, Bojar M, Steiner I; EFNS Task Force. EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. Eur J Neurol 2008;15:649-59.
6. Tunkel AR, Hartman BJ, Kaplan SL, et al. Infectious Diseases Society of America. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004;39:1267-84.
7. Chapman AS, Bakken JS, Folk SM, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States. MMWR 2006;55(RR-4):1-27.
8. World Health Organization (WHO). Guidelines for the management of sexually transmitted infections. Available at: http://www.who.int/hiv/pub/sti/en/STIGuidelines2003.pdf. Accessed October 2011.
9. Shann F, Barker J, Poore P. Chloramphenicol alone versus chloramphenicol plus penicillin for severe pneumonia in children. Lancet. 1985 Sep 28;2(8457):684-6.
10. Rodriguez WJ, Khan WN, Puig J, et al. Sulbactam/ampicillin vs. chloramphenicol/ampicillin for the treatment of meningitis in infants and children. Rev Infect Dis. 1986 Nov-Dec;8 Suppl 5:S620-9.
11. Nathan N, Borel T, Djibo A, et al. Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study. Lancet. 2005 Jul 23-29;366(9482):308-13.
12. Girgis NI, Abu El-Ella AH, Farid Z, et al. Ceftriaxone alone compared to ampicillin and chloramphenicol in the treatment of bacterial meningitis. Chemotherapy. 1988;34 Suppl 1:16-20.
13. Jacobs RF, Wells TG, Steele RW, Yamauchi T. A prospective randomized comparison of cefotaxime vs ampicillin and chloramphenicol for bacterial meningitis in children. J Pediatr. 1985 Jul;107(1):129-33.
14. Rodriguez WJ, Puig JR, Khan WN, et al. Ceftazidime vs. standard therapy for pediatric meningitis: therapeutic, pharmacologic and epidemiologic observations. Pediatr Infect Dis. 1986 Jul-Aug;5(4):408-15.
15. Marks WA, Stutman HR, Marks MI, et al. Cefuroxime versus ampicillin plus chloramphenicol in childhood bacterial meningitis: a multicenter randomized controlled trial. J Pediatr. 1986 Jul;109(1):123-30.
16. Peltola H, Anttila M, Renkonen OV. Randomised comparison of chloramphenicol, ampicillin, cefotaxime, and ceftriaxone for childhood bacterial meningitis. Lancet. 1989 Jun 10;1(8650):1281-7.
17. Tanaka-Kido J, Ortega L, Santos JI. Comparative efficacies of aztreonam and chloramphenicol in children with typhoid fever. Pediatr Infect Dis J. 1990 Jan;9(1):44-8.
18. Gotuzzo E, Echevarria J, Carrillo C, et al. Randomized comparison of aztreonam and chloramphenicol in treatment of typhoid fever. Antimicrob Agents Chemother. 1994 Mar;38(3):558-62.
19. Girgis NI, Abu El Ella AH, Farid Z, et al. Ceftriaxone compared with a combination of ampicillin and chloramphenicol in the treatment of bacterial meningitis in adults. Drug Exp Res 1987;13:497-500.
20. Johansson O, Cronberg S, Hoffstedt B, et al. Cefuroxime versus ampicillin and chloramphenicol for the treatment of bacterial meningitis. Lancet 1982;1:295-299.
21. Arjyal A, Basnyat B, Koirala S, et al. Gatifloxacin versus chloramphenicol for uncomplicated enteric fever: an open-label, randomised, controlled trial. Lancet Infect Dis 2011;11:445-54.
22. Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, et al; Working Group on Civilian Biodefense. Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA 2002;287(17):2236-52.
23. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM, Whitley RJ, Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303-27.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Macrolides
AHFS Class 081212
February 8, 2012

I. Overview

The macrolides are approved to treat a variety of infections, including dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-13] Most of the agents bind to the 50S subunit of bacterial ribosomes, which inhibits bacterial protein synthesis.[14-15] Fidaxomicin has a unique mechanism of action; it inhibits RNA synthesis by RNA polymerases.[12]

Erythromycin is available in several different pharmaceutical preparations, which were developed to improve the absorption of erythromycin base. Erythromycin/sulfisoxazole is the only combination product in this class. Sulfisoxazole is a sulfonamide, which interferes with bacterial growth by inhibiting the synthesis of dihydrofolic acid. Azithromycin and clarithromycin are structural derivatives of erythromycin. They have a broader spectrum of activity, improved oral absorption, fewer gastrointestinal adverse events, and a more favorable pharmacokinetic profile than erythromycin.[14-15] Resistance to the macrolides is increasing and cross-resistance among the various agents has been documented. Telithromycin is a structural derivative of erythromycin and was designed to treat macrolide-resistant pathogens. The mechanism of action is similar to that of erythromycin and other macrolide antibacterials. However, telithromycin may also inhibit the formation of the 30S ribosomal subunit at high concentrations, in addition to the 50S subunit.[15] Fidaxomicin is a newer macrolide that is approved to treat *Clostridium difficile*-associated diarrhea. It is minimally absorbed after oral administration and has little or no activity against organisms other than clostridia.

The macrolides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Several of the macrolides are available in a generic formulation, with the exception of erythromycin lactobionate, erythromycin stearate, fidaxomicin and telithromycin. This class was last reviewed in August 2009.

Table 1. Macrolides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Azithromycin	extended-release suspension, injection, suspension, tablet	Zithromax®*, Zithromax Tri-Pak®*, Zmax®	azithromycin
Clarithromycin	extended-release tablet, suspension, tablet	Biaxin®*, Biaxin XL®*	clarithromycin, clarithromycin ER
Erythromycin base	delayed-release capsule, coated-particle tablet, delayed-release tablet, tablet	PCE®	erythromycin base
Erythromycin ethylsuccinate	suspension, tablet	E.E.S. 200®, E.E.S. 400®*, EryPed 200®, EryPed 400®	erythromycin ethylsuccinate
Erythromycin ethylsuccinate and sulfisoxazole	suspension	N/A	erythromycin ethylsuccinate and sulfisoxazole
Erythromycin lactobionate	injection	Erythrocin Lactobionate®	none
Erythromycin stearate	tablet	Erythrocin Stearate®	none
Fidaxomicin	tablet	Dificid®	none
Telithromycin	tablet	Ketek®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

The macrolides have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the macrolides that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Macrolides[1-13]

Organism	Azithromycin	Clarithromycin	Erythromycin	Erythromycin/ Sulfisoxazole	Fidaxomicin	Telithromycin
Gram-Positive Aerobes						
Listeria monocytogenes			✔			
Staphylococcus aureus	✔	✔	✔			
Streptococcus agalactiae	✔					
Streptococcus pneumoniae	✔	✔	✔			✔
Streptococcus pyogenes	✔	✔	✔			
Gram-Negative Aerobes						
Bordetella pertussis			✔			
Haemophilus ducreyi	✔					
Haemophilus influenzae	✔	✔	✔	✔		✔
Haemophilus parainfluenzae		✔				
Helicobacter pylori		✔				
Legionella pneumophila	✔		✔			
Moraxella catarrhalis	✔	✔				✔
Neisseria gonorrhoeae	✔		✔			
Anaerobes						
Clostridium difficile					✔	
Corynebacterium diphtheriae			✔			
Corynebacterium minutissimum			✔			
Miscellaneous Organisms						
Entamoeba histolytica			✔			
Chlamydia trachomatis	✔		✔			
Chlamydophila pneumoniae	✔	✔				✔
Mycobacterium avium	✔	✔				
Mycobacterium intracellulare	✔	✔				
Mycoplasma hominis	✔					
Mycoplasma pneumoniae	✔	✔	✔			✔
Treponema pallidum			✔			
Ureaplasma urealyticum			✔			

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the macrolides are summarized in Table 3.

Table 3. Treatment Guidelines Using the Macrolides

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Guidelines on the Prevention, Diagnosis, and Treatment of Infective Endocarditis[111] (2009)**	• Antibiotic treatment of infective endocarditis due to oral streptococci and group D streptococci: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin or ceftriaxone for 4 weeks ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for 2 weeks ▪ Vancomycin for 4 weeks (in beta-lactam allergic patients) o Penicillin-resistant strains: ▪ Penicillin G or amoxicillin for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks plus gentamicin for 2 weeks (in beta-lactam allergic patients) • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for 4 to 6 weeks plus gentamicin for 3 to 5 days ▪ Vancomycin for 4 to 6 weeks plus gentamicin for 3 to 5 days (penicillin-allergic patients or methicillin-resistant staphylococci) o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks ▪ Vancomycin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks (penicillin-allergic patients or methicillin-resistant staphylococci) • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains ▪ Amoxicillin plus gentamicin for 4 to 6 weeks ▪ Ampicillin plus gentamicin for 4 to 6 weeks ▪ Vancomycin plus gentamicin for 6 weeks • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months ▪ Doxycycline plus quinolone for >18 months o *Bartonella* species: ▪ Ceftriaxone or ampicillin IV ▪ Doxycycline orally for 6 weeks plus gentamicin or netilmicin for 3 weeks o *Legionella* species: ▪ Erythromycin IV for 2 weeks, then orally for 4 weeks plus rifampin or ciprofloxacin orally for 6 weeks

Clinical Guideline	Recommendation(s)
	o *Mycoplasma* species: ▪ Newer fluoroquinolones for >6 months o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Penicillin G or streptomycin IV for 2 weeks, then cotrimoxazole orally for 1 year ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis (before or without pathogen identification): o Native valves: ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks o Prosthetic valves (early, <12 months post surgery) ▪ Vancomycin IV for 6 weeks, gentamicin IV for 2 weeks, and rifampin orally for 2 weeks o Prosthetic valves (late, ≥12 months post surgery) ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks
American College of Cardiology (ACC)/American Heart Association (AHA): **2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease[29] (2008)**	<u>Rheumatic Fever Prophylaxis</u> • Primary prevention of rheumatic heart disease: o Penicillin G benzathine IM once or penicillin V orally for 10 days o Erythromycin estolate or erythromycin ethylsuccinate orally for 10 days, or azithromycin orally for 5 days in patients who are allergic to penicillin • Secondary prevention of rheumatic fever: o Penicillin G benzathine IM every 4 weeks, or penicillin V orally twice daily, or sulfadiazine orally once daily o Erythromycin orally twice daily for patients who are allergic to penicillin <u>Endocarditis Prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with CHD o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30-60 minutes before procedure): o Oral: amoxicillin o Unable to take oral medications: Ampicillin, cefazolin or ceftriaxone o Allergic to penicillin or ampicillin (oral): cephalexin,

Clinical Guideline	Recommendation(s)
	clindamycin, or azithromycin o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis* o Penicillin G or ceftriaxone for 4 weeks o Ceftriaxone plus gentamicin for 2 weeks o Vancomycin for 4 weeks in patients allergic to penicillin • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin o Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2 weeks o Vancomycin for 4 weeks in patients allergic to penicillin • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin o Ampicillin for 4 to 6 weeks or penicillin G plus gentamicin for 4 to 6 weeks o Vancomycin plus gentamicin for 6 weeks in patients allergic to penicillin • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials o Oxacillin-susceptible strains ▪ Nafcillin or oxacillin for 6 weeks plus the optional addition of gentamicin for 3 to 5 days ▪ Cefazolin for 6 weeks with the optional addition of gentamicin in patients allergic to penicillin o Oxacillin-resistant strains ▪ Vancomycin for 6 weeks o Oxacillin-resistant strains • Therapy for prosthetic valve endocarditis caused by staphylococci o Oxacillin-susceptible strains ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks o Oxacillin-resistant strains ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks • Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms o Ceftriaxone for 4 weeks o Ampicillin-sulbactam for 4 weeks o Ciprofloxacin for 4 weeks • Therapy for culture-negative endocarditis including *Bartonella* endocarditis o Native valve ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for 4 to 6 weeks o Prosthetic valve (early; ≤1 year) ▪ Vancomycin for 6 weeks, plus gentamicin for 2 weeks, plus cefepime for 6 weeks, plus rifampin for 6 weeks o Prosthetic valve (late; >1 year) ▪ Suspected *Bartonella*, culture negative • Ceftriaxone for 6 weeks plus gentamicin with/without doxycycline for 6 weeks ▪ Documented *Bartonella*, culture positive

Clinical Guideline	Recommendation(s)
	• Doxycycline for 6 weeks plus gentamicin for 2 weeks
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines: Management of Encephalitis[114] (2008)**	Empirical Therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or trimethoprim-sulfamethoxazole is recommended • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; trimethoprim-sulfamethoxazole is an alternative in the penicillin-allergic patient • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered • *Tropheryma whipplei:* ceftriaxone, followed by either trimethoprim-sulfamethoxazole or cefixime, is recommended Rickettsioses and Ehrlichioses • *Anaplasma phagocytophilum:* doxycycline is recommended • *Ehrlichia chaffeensis:* doxycycline is recommended • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative Protozoa • *Acanthamoeba:* trimethoprim-sulfamethoxazole plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; trimethoprim-sulfamethoxazole alone and pyrimethamine plus either atovaquone, clarithromycin, azithromycin, or dapsone are alternatives • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative

Clinical Guideline	Recommendation(s)
	• *Trypanosoma brucei rhodesiense:* melarsoprol is recommended

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections[16] (2005)**	Overview
	• Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first- or second-generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of methicillin-resistant S*taphylococcus aureus* (MRSA) strains.
	Animal Bites
	• First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *P. multocida* and should be avoided.
	Animal Contact
	• Anthrax:
	  o No randomized, controlled trials of therapy of cutaneous anthrax exist. Most published data indicate that penicillin is effective therapy and will "sterilize" most lesions between a few hours to 3 days but does not accelerate healing. Its value seems to be primarily in reducing mortality from as high as 20% to 0%.
	  o On the basis of even less evidence, tetracyclines, chloramphenicol, and erythromycin appear to be effective.
	• Cat-scratch disease:
	  o If antimicrobial therapy is used, patients weighing >45.5 kg (>100 lbs) should receive 500 mg of azithromycin orally on day 1, followed by 250 mg once daily for 4 additional days. Those weighing less than the weight listed above should receive 10 mg/kg orally on day 1, followed by 5 mg/kg on days 2–5.
	• Cutaneous bacillary angiomatosis:
	  o Treatment has not been systematically examined. On the basis of results of case reports and small series, erythromycin and doxycycline appear to be effective.
	Cellulitis
	• A large percentage of patients can receive oral medications from the start. Suitable agents include dicloxacillin, cephalexin, clindamycin, or erythromycin, unless streptococci or staphylococci.
	Impetigo
	• The decision of how to treat impetigo depends on the number of lesions, their location (face, eyelid, or mouth), and the need to limit spread of infection to others.
	• Patients who have numerous lesions or who are not responding to topical agents should receive oral antimicrobials effective against both *S. aureus* and *S. pyogenes.*
	• Because *S. aureus* currently accounts for most cases of bullous impetigo, penicillinase-resistant penicillins or first generation cephalosporins are preferred.
	• Erythromycin has been a mainstay of pyoderma therapy, but its utility may be lessened in areas where erythromycin-resistant strains of *S. aureus,* or more recently.

Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for *Clostridium difficile***	Treatment of *Clostridium difficile* infections (CDI) • Discontinue therapy with the inciting antimicrobial agent(s) as soon as possible, as this may influence the risk of CDI recurrence. • When severe or complicated CDI is suspected, initiate empirical treatment as soon as the diagnosis is suspected. • If possible, avoid use of antiperistaltic agents, as they may obscure

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Infection in Adults[109] (2010)	symptoms and precipitate toxic megacolon. • Metronidazole is the drug of choice for the initial episode of mild-to-moderate CDI. The dosage is 500 mg orally 3 times per day for 10–14 days. • Vancomycin is the drug of choice for an initial episode of severe CDI. The dosage is 125 mg orally 4 times per day for 10–14 days. • Vancomycin administered orally with or without intravenously administered metronidazole is the regimen of choice for the treatment of severe, complicated CDI. The vancomycin dosage is 500 mg orally 4 times per day and 500 mg in approximately 100 mL normal saline per rectum every 6 hours as a retention enema, and the metronidazole dosage is 500 mg intravenously every 8 hours. • Treatment of the first recurrence of CDI is usually with the same regimen as for the initial episode but should be stratified by disease severity (mild-to-moderate, severe, or severe complicated), as is recommended for treatment of the initial CDI episode. • Do not use metronidazole beyond the first recurrence of CDI or for long-term chronic therapy because of potential for cumulative neurotoxicity. • Treatment of the second or later recurrence of CDI with vancomycin therapy using a tapered and/or pulse regimen is the preferred next strategy. • No recommendations can be made regarding prevention of recurrent CDI in patients who require continued antimicrobial therapy for the underlying infection.

European Society of Clinical Microbiology and Infectious Diseases (ESCMID): **Treatment Guidance Document for *Clostridium difficile* Infection (CDI)[110] (2009)**	Treatment of *Clostridium difficile* infection (CDI)
	• Treatment for an initial episode and a first recurrence of CDI:
	  o If oral therapy is possible: metronidazole 500 mg three times a day for 10 days (non-severe); vancomycin 125 mg four times a day for 10 days (severe).
	  o If oral therapy is impossible: metronidazole 500 mg intravenously three times a day for 10 days (non-severe); metronidazole 500 mg intravenously three times a day for 10 days plus intracolonic vancomycin 500 mg in 100 ml of normal saline every 4 to 12 hours and/or vancomycin 500 mg via nasogastric tube four times a day (severe).
	• Treatment for a second recurrence of CDI and later recurrence:
	  o If oral therapy is possible: vancomycin 125 mg four times a day for 10 days; also consider a taper or pulse strategy.
	  o If oral therapy is impossible: metronidazole 500 mg intravenously three times a day for 10-14 days plus retention enema of vancomycin 500 mg in 100 ml normal saline every 4 to 12 hours and/or vancomycin 500 mg by nasogastric tube four times a day.
	• In all the above-mentioned cases, oral vancomycin may be replaced by teicoplanin 100 mg twice daily.

World Gastroenterology Organization (WGO): **Acute Diarrhea[118] (2008)**	General Considerations
	• Antimicrobials are the drugs of choice for empirical treatment of traveler's diarrhea and of community-acquired secretory diarrhea when the pathogen is known.
	• Consider antimicrobial treatment for:
	  o Persistent *Shigella*, *Salmonella*, *Campylobacter*, or parasitic infections
	  o Infections in the aged, immunocompromised patients, and patients with impaired resistance, sepsis, or with prostheses

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	o Moderate/severe traveler's diarrhea or diarrhea with fever and/or with bloody stools (quinolones as initial therapy or co-trimoxazole as a second choice) • Nitazoxanide may be appropriate for *Cryptosporidium* and other infections, including some bacteria. • Rifaximin may also be useful. <u>Antimicrobial Agents for the Treatment of Specific Causes of Diarrhea</u> • Cholera o First-line: doxycycline or tetracycline o Alternative: azithromycin or ciprofloxacin • Shigellosis o First-line: ciprofloxacin o Alternative: pivmecillinam or ceftriaxone • Amebiasis o First-line: metronidazole • Giardiasis o First-line: metronidazole • *Campylobacter* o First-line: azithromycin
Infectious Diseases Society of America (IDSA): **The Practice of Travel Medicine[117] (2006)**	<u>Chemoprophylaxis</u> • Bismuth subsalicylate–containing formulations and antibiotics have been proven effective in preventing traveler's diarrhea. • Probiotics, such as lactobacillus, have not demonstrated sufficient efficacy to be recommended. • Widespread drug resistance renders doxycycline and trimethoprim-sulfamethoxazole (TMP-SMX) no longer useful for prevention of traveler's diarrhea. • Chemoprophylaxis can contribute to development of resistant enteric bacteria and potentially predispose the traveler to infection with other deleterious pathogens, such as *Clostridium difficile.* • The routine use of antibiotic prophylaxis for travelers' diarrhea is not generally recommended. • Chemoprophylaxis may be considered in healthy travelers for whom staying well is critical and in special-needs travelers in whom the risk for diarrhea is increased or the consequences of a diarrheal episode may be severe. • When considering chemoprophylaxis, fluoroquinolone antibiotics remain the first choice. • Chemoprophylaxis should be recommended for no more than 2–3 weeks. <u>Treatment</u> • Fluid replacement and a diet restricted to liquids and bland foods may be appropriate, though they may not provide additional benefits beyond antibiotic treatment. • Symptomatic therapy with bismuth subsalicylate may be recommended in mild cases of diarrhea, but better agents exist for moderate-to-severe disease. • Loperamide has become the antimotility agent of choice. It is more efficacious in controlling diarrhea than bismuth subsalicylate and has an onset of action within the first 4 hours after ingestion. When it is used in combination with an antibiotic, there may be rapid improvement of traveler's diarrhea. • Antibiotics are effective in the treatment of traveler's diarrhea and can reduce the average duration of disease from several days to ~1 day. • Antibiotics that are recommended include fluoroquinolones

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	(norfloxacin, ciprofloxacin, ofloxacin, levofloxacin), azithromycin, and rifaximin. • Fluoroquinolones remain predictably active for empiric therapy in most parts of the world and remain the drugs of first choice. • Antibiotics that are no longer recommended because of drug resistance worldwide are the sulfonamides, neomycin, ampicillin, doxycycline, tetracycline, trimethoprim alone, and TMP-SMX.
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Infectious Diarrhea[116] (2001)**	Recommendations for Therapy Against Specific Pathogens • *Shigella* species: o Trimethoprim-sulfamethoxazole (TMP-SMZ) o Fluoroquinolone o Nalidixic acid o Ceftriaxone o Azithromycin • *Salmonella,* non-typhi species: o Treatment is not routinely recommended; however, consider therapy in patients <6 months old or >50 years old, or patients that have a prosthesis, valvular heart disease, severe atherosclerosis, malignancy, or uremia. o TMP-SMZ o Fluoroquinolone • *Campylobacter* species o Erythromycin • *Escherichia coli* species o TMP-SMZ o Fluoroquinolone • *Aeromonas* or *Plesiomonas* species o TMP-SMZ o Fluoroquinolone • *Yersinia* species o Antibiotic therapy is not usually required. For severe infections or associated bacteremia, combination therapy with doxycycline, aminoglycosides TMP-SMZ or a fluoroquinolone is recommended. • *Vibrio cholerae* o Doxycycline or tetracycline o Fluoroquinolone • Toxigenic *Clostridium difficile* o Metronidazole • *Isospora* species o TMP-SMZ • *Cyclospora* species o TMP-SMZ
American College of Gastroenterology (ACG): **Guideline on the Management of *Helicobacter pylori* Infection[30] (2007)**	• The recommended primary therapies for *H. pylori* infection include: a PPI, clarithromycin, and amoxicillin, or metronidazole (clarithromycin-based triple therapy) for 14 days or a PPI or H2RA, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10–14 days.
Canadian Helicobacter Study Group Consensus Conference: **Update on the Management of *Helicobacter pylori*[31] (2004)**	• A quadruple combination of a PPI, bismuth, tetracycline, and metronidazole for 10-14 days can be considered first-line therapy for the eradication of *H. pylori.* • Eradication rates with the recommended quadruple therapy are comparable with those achieved with PPI-based triple therapy regimens in patients who adhere to the protocol. Given the lower

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	number of tablets and twice daily dosing, in practice, PPI-based triple therapy may be the first choice.
European *Helicobacter pylori* Study Group: **Current Concepts in the Management of *H. pylori* Infection–The Maastricht 2-2000 Consensus Report[32] (2002)**	• First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole. • Second-line therapy should use quadruple therapy with a PPI, bismuth, metronidazole, and tetracycline. • When bismuth is not available, second-line therapy should be triple therapy with a proton-pump inhibitor.
Canadian Dyspepsia Working Group: **An Evidence-Based Approach to the Management of Uninvestigated Dyspepsia in the Era of *Helicobacter pylori*[33] (2000)**	• First-line eradication therapies for *H. pylori* are triple therapies of a PPI plus amoxicillin plus clarithromycin (PPI + AC), or a PPI plus metronidazole plus clarithromycin (PPI + MC), twice daily for 1 week; or ranitidine bismuth citrate plus either AC or MC. • If the first eradication therapy has failed, the action recommended by the Canadian *Helicobacter pylori* Consensus Conference is to use a different first-line therapy than that used initially (e.g., switch from PPI + AC to PPI + MC). • An alternative therapy is a 14-day quadruple regimen of a PPI plus bismuth plus metronidazole plus tetracycline (PPI + BMT). • For the management of patients negative for *H. pylori*, a PPI is the first-line therapy choice.
Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines[17] (2010)**	<u>Chancroid</u> • Recommended regimens: o Azithromycin 1 g orally in a single dose o Ceftriaxone 250 mg intramuscularly (IM) in a single dose o Ciprofloxacin 500 mg orally twice a day for 3 days o Erythromycin base 500 mg orally three times a day for 7 days <u>Granuloma Inguinale (Donovanosis)</u> • Recommended regimen: o Doxycycline 100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed • Alternative regimens: o Azithromycin 1 g orally once per week for at least 3 weeks and until all lesions have completely healed o Ciprofloxacin 750 mg orally twice a day for at least 3 weeks and until all lesions have completely healed o Erythromycin base 500 mg orally four times a day for at least 3 weeks and until all lesions have completely healed o Trimethoprim-sulfamethoxazole one double-strength (160 mg/800 mg) tablet orally twice a day for at least 3 weeks and until all lesions have completely healed • The addition of an aminoglycoside (e.g., gentamicin 1 mg/kg IV every 8 hours) to these regimens can be considered if improvement is not evident within the first few days of therapy. <u>Lymphogranuloma Venereum</u> • Recommended regimen: o Doxycycline 100 mg orally twice a day for 21 days • Alternative regimen: o Erythromycin base 500 mg orally four times a day for 21 days <u>Nongonococcal Urethritis</u> • Recommended regimens: o Azithromycin 1 g orally in a single dose o Doxycycline 100 mg orally twice a day for 7 days • Alternative regimens: o Erythromycin base 500 mg orally four times a day for 7 days

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	o Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days o Levofloxacin 500 mg orally once daily for 7 days o Ofloxacin 300 mg orally twice a day for 7 days Recurrent and Persistent Urethritis • Recommended regimens: o Metronidazole 2 g orally in a single dose o Tinidazole 2 g orally in a single dose plus azithromycin 1 g orally in a single dose (if not used for initial episode) Cervicitis • Recommended regimens for presumptive treatment: o Azithromycin 1 g orally in a single dose o Doxycycline 100 mg orally twice a day for 7 days Chlamydial Infections • Recommended regimens: o Azithromycin 1 g orally in a single dose o Doxycycline 100 mg orally twice a day for 7 days • Alternative regimens: o Erythromycin base 500 mg orally four times a day for 7 days o Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days o Levofloxacin 500 mg orally once daily for 7 days o Ofloxacin 300 mg orally twice a day for 7 days Ophthalmia Neonatorum Caused by *C. trachomatis* • Recommended regimen: o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days Chlamydial Infections Among Children • Recommended regimen for children <45 kg: o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days • Recommended regimen for children ≥45 kg and <8 years of age: o Azithromycin 1 g orally in a single dose • Recommended regimens for children ≥8 years of age: o Azithromycin 1 g orally in a single dose o Doxycycline 100 mg orally twice a day for 7 days Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum • Recommended regimens: o Ceftriaxone 250 mg IM in a single dose o Cefixime 400 mg orally in a single dose o Single-dose injectable cephalosporin regimens plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for 7 days Uncomplicated Gonococcal Infections of the Pharynx • Recommended regimens: o Ceftriaxone 250 mg IM in a single dose plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for 7 days
American Academy of Pediatrics (AAP)/American Academy of Family Physicians (AAFP): **Diagnosis and Management of Acute Otitis Media[18] (2004)**	Observation Option • Observation without use of antibacterial agents in a child with uncomplicated acute otitis media (AOM) is an option for selected children based on diagnostic certainty, age, illness severity, and assurance of follow-up. The "observation option" for AOM refers to deferring antibacterial treatment of selected children for 48 to 72 hours and limiting management to symptomatic relief. This option should be

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	limited to otherwise healthy children 6 months to 2 years of age with non-severe illness at presentation and an uncertain diagnosis and to children 2 years of age and older without severe symptoms at presentation or with an uncertain diagnosis.
	<u>Antibacterial Options - Temperature <39°C Without Severe Otalgia</u>
	• Initial Treatment With Antibacterial Agents
	  o Recommended agent
	  ▪ Amoxicillin 80-90 mg/kg/day
	  o Alternative for penicillin allergy
	  ▪ Type I: azithromycin, clarithromycin
	• Treatment failure at 48-72 hours after initial management with observation option
	  o Recommended agent
	  ▪ Amoxicillin 80-90 mg/kg/day
	  o Alternative for penicillin allergy
	  ▪ Type I: azithromycin, clarithromycin
	• Treatment failure at 48-72 hours after initial management with antibacterial agents
	  o Recommended agent
	  ▪ Amoxicillin-clavulanate (90 mg/kg/day of amoxicillin component, with 6.4 mg/kg/day of clavulanate).
	  o Alternative for penicillin allergy
	  ▪ Type I: clindamycin
	<u>Antibacterial Options - Temperature ≥39°C and/or Severe Otalgia</u>
	• Initial treatment with antibacterial agents
	  o Recommended agent
	  ▪ Amoxicillin-clavulanate (90 mg/kg/day of amoxicillin component, with 6.4 mg/kg/day of clavulanate).
	  o Alternative for penicillin allergy
	  ▪ Ceftriaxone for 1 or 3 days
	• Treatment failure at 48-72 hours after initial management with observation option
	  o Recommended agent
	  ▪ Amoxicillin-clavulanate (90 mg/kg/day of amoxicillin component, with 6.4 mg/kg/day of clavulanate).
	  o Alternative for penicillin allergy
	  ▪ Ceftriaxone for 1 or 3 days
	• Treatment failure at 48-72 hours after initial management with antibacterial agents
	  o Recommended agent
	  ▪ Ceftriaxone for 3 days
	  o Alternative for penicillin allergy
	  ▪ Tympanocentesis, clindamycin

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Group A Streptococcal Pharyngitis[19] (2002)**	• Patients with acute streptococcal pharyngitis should receive therapy with an antimicrobial agent in a dose and for a duration that is likely to eradicate the infecting organism from the pharynx. • Penicillin remains the agent of choice because of its proven efficacy, safety, and narrow spectrum. • Erythromycin is a suitable alternative for patients allergic to penicillin.
American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF): **Clinical**	<u>Symptomatic Relief of Viral Rhinosinusitis (VRS)</u> • Management of VRS is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively.

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Practice Guideline: Adult Sinusitis[112] (2007)	• Topical or systemic decongestants may offer additional symptomatic relief. • Antihistamines have been used to treat VRS due to their drying effect; however, no studies have been published that assess the impact of antihistamines specifically on VRS outcomes. Adverse effects of antihistamines, especially first-generation H_1-antagonists, include drowsiness, behavioral changes, and impaired mucus transport in the nose and sinuses because of drying. Symptomatic Relief of Acute Bacterial Rhinosinusitis (ABRS) • Symptomatic treatments for ABRS include decongestants, corticosteroids, saline irrigation, and mucolytics. None of these products have been approved by the FDA for use in acute rhinosinusitis, and few have data from controlled clinical studies supporting this use. • Antihistamines have no role in the symptomatic relief of ABRS in nonatopic patients. There are no studies that support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. • Antihistamines may be considered in patients with ABRS whose symptoms suggest a significant allergic component. Watchful Waiting for Acute Bacterial Rhinosinusitis (ABRS) • Observation without use of antibiotics is an option for selected adults with uncomplicated ABRS who have mild illness (mild pain and temperature <38.3°C or 101°F). Choice of Antibiotic for Acute Bacterial Rhinosinusitis (ABRS) • If a decision is made to treat ABRS with an antibiotic, the clinician should prescribe amoxicillin as first-line therapy for most adults. Treatment Failure for Acute Bacterial Rhinosinusitis (ABRS) • If the patient worsens or fails to improve with the initial management option by 7 days after diagnosis, the clinician should reassess the patient to confirm ABRS, exclude other causes of illness, and detect complications. • If ABRS is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI): **The Diagnosis and Management of Sinusitis: An Updated Practice Parameter[20] (2005)**	• Antibiotics are the primary therapy for bacterial sinusitis. Choice of antibiotic should be based on predicted effectiveness and side effects. • Amoxicillin is a reasonable initial antibiotic choice in both children and adults with uncomplicated disease. • Trimethoprim-sulfamethoxazole can be used as an alternative drug in adults. • For patients allergic to or intolerant of amoxicillin, alternatives include cephalosporins, macrolides, or quinolones. • Acute sinusitis generally responds to treatment for 10 to 14 days. Some physicians continue treatment for 7 days after the patient is well to ensure complete eradication of the organism and prevent relapse.
American Academy of Pediatrics (AAP): **Clinical Practice Guideline: Management of Sinusitis[21] (2001)**	• Antibiotics are recommended for the management of acute bacterial sinusitis to achieve a more rapid clinical cure. • For children younger than 2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in degree of severity, who do not attend day care, and have not recently been treated with an antimicrobial, amoxicillin is recommended. • In cases of serious allergic reactions, clarithromycin or azithromycin can be used in an effort to select an antimicrobial of an entirely

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	different class. • Recent pneumococcal surveillance studies indicate that resistance to trimethoprim-sulfamethoxazole and erythromycin-sulfisoxazole is substantial. When patients fail to improve while receiving amoxicillin, trimethoprim-sulfamethoxazole and erythromycin-sulfisoxazole are not appropriate choices for antimicrobial therapy.
American College of Chest Physicians (ACCP): **Chronic Cough Due to Acute Bronchitis, ACCP Evidence-Based Clinical Practice Guidelines[23] (2006)**	• For patients with the putative diagnosis of acute bronchitis, routine treatment with antibiotics is not justified and should not be offered.
American College of Chest Physicians (ACCP): **Chronic Cough Due to Chronic Bronchitis, ACCP Evidence-Based Clinical Practice Guidelines[24] (2006)**	• In stable patients with chronic bronchitis, there is no role for long-term prophylactic therapy with antibiotics. • In patients with acute exacerbations of chronic bronchitis, the use of antibiotics is recommended; patients with severe exacerbations and those with more severe airflow obstruction at baseline are the most likely to benefit.

Global Initiative for Chronic Obstructive Lung Disease (GOLD): **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[22] (2010)**	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in COPD.
	• There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful.
	• Based on current available evidence, antibiotics should be given to:
	  o Patients with exacerbations of COPD with the following three cardinal symptoms: dyspnea, sputum volume, and sputum purulence.
	  o Patients with exacerbations of COPD with two of the cardinal symptoms, if the increased purulence of sputum is one of the two symptoms.
	  o Patients with a severe exacerbation of COPD that requires mechanical ventilation (invasive or noninvasive).
	• Antibiotic treatment in exacerbations of COPD:
	  o Group A (mild exacerbation; no risk factors for poor outcome)
	  ▪ Recommended oral treatment: β-lactam (penicillin, ampicillin, amoxicillin), tetracycline, or trimethoprim-sulfamethoxazole
	  ▪ Alternative oral treatment: β-lactam/β-lactamase inhibitor, macrolides, second or third generation cephalosporin, or ketolides
	  o Group B (moderate exacerbation with risk factor(s) for poor outcome)
	  ▪ Recommended oral treatment: β-lactam/β-lactamase inhibitor
	  ▪ Alternative oral treatment: fluoroquinolones (gemifloxacin, levofloxacin, moxifloxacin)
	  ▪ Parenteral treatment: β-lactam/β-lactamase inhibitor, second or third generation cephalosporin, or fluoroquinolones (levofloxacin, moxifloxacin)
	  o Group C (severe exacerbation with risk factors for *P. aeruginosa* infection)
	  ▪ Recommended oral treatment: fluoroquinolones (ciprofloxacin, levofloxacin)

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	▪ Parenteral treatment: fluoroquinolones (ciprofloxacin, levofloxacin) or β-lactam with *P. aeruginosa* activity
Center for Disease Control and Prevention (CDC): **Recommended Antimicrobial Agents for the Treatment and Postexposure Prophylaxis of Pertussis[27] (2005)**	• Macrolides (erythromycin, clarithromycin, and azithromycin) are preferred for the treatment of pertussis in patients >1 month of age. For infants aged <1 month, azithromycin is preferred; erythromycin and clarithromycin are not recommended. • For treatment of patients >2 months of age, an alternative agent to macrolides is trimethoprim-sulfamethoxazole (TMP–SMZ). • The choice of antimicrobial should take into account effectiveness, safety, tolerability, and ease of adherence to the regimen. • Azithromycin and clarithromycin are as effective as erythromycin for treatment of pertussis in patients aged >6 months, are better tolerated, and are associated with fewer and milder side effects than erythromycin. • Erythromycin and clarithromycin, but not azithromycin, are inhibitors of the cytochrome P450 enzyme system (CYP3A subclass) and can interact with other drugs that are metabolized by this system. • Azithromycin and clarithromycin are more resistant to gastric acid, achieve higher tissue concentrations, and have a longer half-life than erythromycin, allowing less frequent administration (1–2 doses per day) and shorter treatment regimens (5–7 days).

Infectious Diseases Society of America (IDSA): **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age[113] (2011)**	<u>Outpatient Treatment</u>
	• Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia (CAP), because viral pathogens are responsible for the great majority of clinical disease.
	• Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate CAP suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*.
	• For patients allergic to amoxicillin, the following agents are considered alternative treatment options:
	  o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil)
	  o Levofloxacin (oral therapy)
	  o Linezolid (oral therapy)
	• Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with CAP caused by atypical pathogens.
	<u>Inpatient Treatment</u>
	• Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with CAP when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *S. pneumoniae*.
	• Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema.
	• Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America.

Clinical Guideline	Recommendation(s)
	• Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *M. pneumoniae* and *C. pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *S. aureus*.

Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS): **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults[25] (2007)**	<u>Empirical Antimicrobial Therapy</u>
	• Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.
	• Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.
	• Outpatient treatment
	  o Previously healthy and no risk factors for drug-resistant *S. pneumoniae* (DRSP) infection:
	  ▪ Macrolide (azithromycin, clarithromycin, or erythromycin)
	  ▪ Doxycycline
	  o Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected); or other risks for DRSP infection:
	  ▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin)
	  ▪ β-lactam plus a macrolide (High-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide.)
	  o In regions with a high rate of infection with high-level macrolide-resistant *S. pneumoniae,* consider the use of alternative agents listed above for any patient, including those without comorbidities.
	• Inpatient, non-ICU treatment
	  o Respiratory fluoroquinolone
	  o β-lactam plus a macrolide (Preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients).
	• Inpatient, ICU treatment
	  o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended.)
	  o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above)

Clinical Guideline	Recommendation(s)
	plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam). o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.
American College of Chest Physicians (ACCP): **Management of Community-Acquired Pneumonia in the Home: An American College of Chest Physicians Clinical Position Statement[26] (2005)**	• Antibiotic choice and route of administration are central to an appropriate in-home treatment plan. The oral route is recommended if the patient can tolerate it, and if the availability and activity of the agent are adequate. • Although treatment is facilitated if the etiologic agent is known (pathogen-directed treatment for CAP is provided in the IDSA guidelines), most outpatient treatment is empiric. • The use of a macrolide, doxycycline, or fluoroquinolone agent, as recommended both by the IDSA and the ATS guidelines, may be appropriate empiric outpatient treatment for low-risk patients (i.e., otherwise young healthy individuals). Alternatives to these agents in low-risk patients are amoxicillin/clavulanate and some second-generation cephalosporins (e.g., cefuroxime, cefpodoxime, or cefprozil). • A lack of response to treatment with macrolides and fluoroquinolones has been reported. Some authorities prefer to reserve the use of fluoroquinolones for older patients, patients who are allergic or intolerant to macrolides, patients who have recently received macrolide treatment, patients with comorbidities, patients with documented infections with highly resistant pneumococci, or patients with a lack of response to treatment with another agent.
Centers for Disease Control and Prevention (CDC)/National Institutes of Health (NIH)/ HIV Medicine Association of the Infectious Diseases Society of America (HIVMA/IDSA): **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents[28] (2008)**	Preventing Disseminated *Mycobacterium avium* Complex Disease • HIV-infected adults and adolescents should receive chemoprophylaxis against disseminated MAC disease if they have a CD4+ count of <50 cells/μL. • Azithromycin or clarithromycin are the preferred prophylactic agents. • The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used. • The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared with azithromycin alone do not warrant a routine recommendation for this regimen. • Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. • If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for MAC disease, although drug interactions may make this agent difficult to use. • Primary MAC prophylaxis should be discontinued among adult and adolescent patients who have responded to ART with an increase in CD4+ counts to >100 cells/μL for ≥3 months. Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/μL. Treatment of Disseminated *Mycobacterium avium* Complex Disease • Initial treatment of MAC disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance. • Clarithromycin is the preferred first agent; however, azithromycin can be substituted for clarithromycin when drug interactions or

Clinical Guideline	Recommendation(s)
	clarithromycin intolerance preclude the use of clarithromycin. • Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients.
Surgical Infection Prevention Guideline Writers Workgroup (SIPGWW): **Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project[115] (2004)**	General Considerations • There is published evidence to support the use of many prophylactic antimicrobial regimens besides those included in this advisory statement or in existing guidelines. • Factors such as cost, half-life, safety, and antimicrobial resistance favor the use of older agents with a relatively narrow spectrum. • The use of newer, broad-spectrum drugs that are front-line therapeutic agents should be avoided in surgical prophylaxis to reduce emergence of bacterial strains that are resistant to these antimicrobials. Gynecologic and Obstetrical Surgery • For abdominal or vaginal hysterectomy, cefotetan is preferred, but reasonable alternatives are cefazolin and cefoxitin. In cases of β-lactam allergy, the workgroup recommends the use of one of the following regimens: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; metronidazole combined with gentamicin or ciprofloxacin; or clindamycin monotherapy. A single 750-mg dose of levofloxacin can be substituted for ciprofloxacin. • For cesarean section, a narrow-spectrum antimicrobial regimen similar to that recommended for hysterectomy provides adequate prophylaxis. Orthopedic Total Joint (Hip and Knee) Arthroplasty • The preferred antimicrobials for prophylaxis in patients undergoing hip or knee arthroplasty are cefazolin and cefuroxime. • Vancomycin or clindamycin may be used in patients with serious allergy or adverse reactions to β-lactams. Cardiothoracic and Vascular Surgery • The recommended antimicrobials for cardiothoracic and vascular operations include cefazolin or cefuroxime. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin is appropriate, and clindamycin may be an acceptable alternative. Colorectal Surgery • Antimicrobial prophylaxis for colorectal operations can consist of an orally administered antimicrobial bowel preparation, a preoperative parenteral antimicrobial, or the combination of both. • Recommended oral prophylaxis consists of neomycin plus erythromycin or neomycin plus metronidazole, initiated no more than 18–24 h before the operation, along with administration of a mechanical bowel preparation. • Cefotetan or cefoxitin are recommended for parenteral prophylaxis, and the combination of parenteral cefazolin and metronidazole is also recommended as an alternative. • For patients with confirmed allergy or adverse reaction to β-lactams, use of one of the following regimens is recommended: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; or metronidazole combined with gentamicin or ciprofloxacin. A single 750-mg dose of levofloxacin can be substituted for ciprofloxacin.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the macrolides are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Macrolides[1-13]

Indication	Azithromycin	Clarithromycin	Erythromycin	Erythromycin/ Sulfisoxazole	Fidaxomicin	Telithromycin
Dermatological Infections						
Erythrasma			✔			
Skin and skin-structure infections	✔ †	✔ §	✔			
Gastrointestinal Infections						
Treatment of *Clostridium difficile*-associated diarrhea					✔	
Treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori* (in combination with amoxicillin and lansoprazole or omeprazole as triple therapy)		✔ §				
Treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori* (in combination with omeprazole or ranitidine bismuth citrate as dual therapy)		✔ §				
Genitourinary Infections						
Chancroid	✔ †					
Pelvic inflammatory disease due to *N. gonorrhoeae*			✔			
Pelvic inflammatory disease due to *C. trachomatis*, *N. gonorrhoeae*, and *M. hominis*	✔ *					
Syphilis			✔			
Urethral, endocervical, or rectal infections			✔			
Urethritis/cervicitis (gonococcal)	✔ †					
Urethritis/cervicitis (non-gonococcal)	✔ † ‖		✔			
Urogenital infections in pregnancy			✔			
Respiratory Infections						
Acute exacerbations of chronic bronchitis	✔ †	✔ §δ				
Legionnaires' disease			✔			
Otitis media	✔ †	✔ §		✔		
Pertussis			✔			
Pharyngitis and/or tonsillitis	✔ †	✔ §	✔			

Indication	Azithromycin	Clarithromycin	Erythromycin	Erythromycin/ Sulfisoxazole	Fidaxomicin	Telithromycin
Pneumonia (community-acquired)	✔ *†‡	✔ §δ	✔			✔
Pneumonia of infancy due to *C. trachomatis*			✔			
Respiratory tract infections (lower)			✔			
Respiratory tract infections (upper)			✔			
Sinusitis	✔ †‡	✔ §δ				
Miscellaneous Infections						
Conjunctivitis of the newborn due to *C. trachomatis*			✔			
Diphtheria			✔			
Intestinal amebiasis			✔ †			
Listeriosis			✔			
Mycobacterial infections due to *M. avium* or *M. intracellulare* (disseminated, treatment)		✔ §				
Mycobacterium avium complex (MAC) disease in patients with advanced HIV infection (disseminated, prevention)	✔ ‖	✔ §				
Mycobacterium avium complex (MAC) disease in patients with advanced HIV infection (disseminated, treatment)	✔ ‖					
Rheumatic fever (prophylaxis)			✔			

δExtended-release formulation
§Immediate-release formulations
*IV formulation
‡Suspension formulation (extended-release)
†Tablet formulation (250 mg and 500 mg) and suspension formulation (immediate-release)
‖Tablet formulation (600 mg) and suspension formulation (1 g packet)

IV. Pharmacokinetics

The pharmacokinetic parameters of the macrolides are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Macrolides[1-13]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Azithromycin	38	7-50	Liver	Renal (12) Biliary (>50)	11-68
Clarithromycin	50	42-50	Liver	Renal (20-40)	3-7
Erythromycin	>35	73-81	Liver	Biliary	1.5-2
Fidaxomicin	Minimal	N/A	Intestine	Feces (>92)	11.7
Sulfisoxazole	100	85-88	Liver	Renal (95)	4-7
Telithromycin	57	60-70	Liver	Renal (12-14) Feces (75)	10-13

V. Drug Interactions

Significant drug interactions with the macrolides are listed in Table 6.

Table 6. Significant Drug Interactions with the Macrolides[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	1	Anticoagulants	Effects of oral anticoagulants may be potentiated. Bleeding may occur. Close monitoring of prothrombin time is recommended.
Macrolides (clarithromycin, erythromycin, telithromycin)	1	Carbamazepine	Increases in plasma carbamazepine concentrations have been observed.
Macrolides (clarithromycin, erythromycin)	1	Cisapride	Torsades des points, QT prolongation, and cardiac arrest are possible due to decreased cisapride metabolism.
Macrolides (clarithromycin, erythromycin telithromycin)	1	Colchicine	Increases in colchicine concentration have been observed due to inhibition of CYP3A4 and P-glycoprotein.
Macrolides (clarithromycin, erythromycin, telithromycin)	1	Cyclosporine	Pharmacologic effects and plasma concentrations of cyclosporine may be increased. Renal and hepatic toxicity may occur.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	1	Digoxin	Increases in serum digoxin concentrations have been observed, resulting in signs of digoxin toxicity.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	1	Disopyramide	Pharmacologic effects of disopyramide may be increased. Elevated disopyramide plasma concentrations may result in toxicity characterized by prolongation of the QRS complex and QT interval, arrhythmias, and

Generic Name(s)	Significance Level	Interaction	Mechanism
			asystole.
Macrolides (clarithromycin, erythromycin, telithromycin)	1	Ergotamine and dihydroergotamine	Reports of acute ergot toxicity characterized by vasospasm and ischemia in the extremities and other tissues, including the central nervous system (CNS) have been reported.
Macrolides (clarithromycin, erythromycin, telithromycin)	1	HMG-CoA reductase inhibitors	Increased concentrations of HMG-CoA reductase inhibitors have been observed. Rhabdomyolysis and liver dysfunction may occur.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	1	Pimozide	Cardiac arrhythmia, QT prolongation, and cardiac arrest are possible due to elevated serum pimozide concentrations. Co-administration is contraindicated.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	1	Sotalol	Sotalol and telithromycin may cause additive QT interval prolongation. The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
Macrolides (clarithromycin, erythromycin, telithromycin)	2	Benzodiazepines	CNS effects such as somnolence and confusion have been reported with the co-administration of these medications.
Macrolides (clarithromycin, erythromycin, telithromycin)	2	Cilostazol	Increased cilostazol exposure has been reported with co-administration. Monitor blood pressure, heart rate, complete blood counts, bleeding time, routine chemistry, and blood glucose for signs of cilostazol toxicity.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	2	Rifamycins	Induction of hepatic microsomal enzymes by rifamycins may increase the metabolic elimination of macrolides. Inhibition of hepatic microsomal enzymes by macrolides may decrease the metabolic elimination of rifamycins.
Macrolides (clarithromycin, telithromycin)	2	Ritonavir	Plasma concentrations of ritonavir and macrolides are increased when the drugs are used concomitantly. Potential QT interval prolongation may occur.
Macrolides (clarithromycin, erythromycin, telithromycin)	2	Sildenafil	Co-administration may result in increased exposure to sildenafil. Reduction of sildenafil doses may be considered.
Macrolides (clarithromycin,	2	Tacrolimus	Macrolides may increase gastrointestinal absorption and

Generic Name(s)	Significance Level	Interaction	Mechanism
erythromycin, telithromycin)			inhibit hepatic and gastrointestinal metabolism of tacrolimus via inhibition of cytochrome P450 3A4. Pharmacologic effects of macrolides and tacrolimus on myocardium may be additive
Macrolides (erythromycin)	2	Theophylline	Inhibition of cytochrome P450 1A2 isoenzymes by erythromycin may decrease the metabolic elimination of theophylline. Elevated theophylline plasma concentrations with toxicity characterized by nausea, vomiting, cardiovascular instability, and seizures may occur.
Sulfisoxazole	2	Anticoagulants	Prothrombin time may be increased. Close monitoring of prothrombin time is recommended.
Sulfisoxazole	2	Methotrexate	Methotrexate may be displaced from plasma protein binding sites. Close monitoring is recommended.
Sulfisoxazole	2	Sulfonylureas	Sulfisoxazole can potentiate the blood sugar lowering effect of sulfonylureas. Close monitoring of blood sugar is recommended.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the macrolides are listed in Table 7. The boxed warning for telithromycin is listed in Table 8.

Table 7. Adverse Drug Events (%) Reported with the Macrolides[1-13]

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Erythromycin/ Sulfisoxazole	Fidaxomicin	Telithromycin
Cardiovascular						
Allergic myocarditis	-	-	-	✔	-	-
Atrial arrhythmias	-	-	-	-	-	✔
Bradycardia	-	-	-	-	-	<1
Chest pain	<1	-	✔	-	-	-
Cyanosis	-	-	-	✔	-	-
Hypotension	✔	-	-	-	-	<1
Palpitations	<1	-	✔	✔	-	✔
Syncope	-	-	-	✔	-	-
Tachycardia	-	-	-	✔	-	-
Torsades de pointes	✔	✔	✔	✔	-	-
Ventricular tachycardia	✔	✔	✔	✔	-	-
Central Nervous System						
Aggressive reactions	✔	-	-	-	-	-
Agitation	✔	-	-	-	-	-
Anxiety	✔	✔	-	✔	-	<1
Asthenia	✔	-	-	-	-	-
Ataxia	-	-	-	✔	-	-
Behavioral changes	-	✔	-	-	-	-
Confusion	-	✔	✔	-	-	✔
Depersonalization	-	✔	-	-	-	-
Depression	-	✔	-	✔	-	-
Disorientation	-	✔	-	✔	-	-
Dizziness	<1	✔	✔	✔	-	2-3
Fever	✔	-	✔	✔	-	-
Hallucinations	-	✔	✔	✔	-	✔
Headache	<1	2	8	✔	-	2-5
Hyperactivity	✔	-	-	✔	-	-
Insomnia	✔	✔	-	✔	-	<2
Intracranial hypertension	-	-	-	✔	-	-
Loss of consciousness	-	-	-	-	-	✔
Manic behavior	-	✔	-	-	-	-

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Erythromycin/ Sulfisoxazole	Fidaxomicin	Telithromycin
Nervousness	✔	-	-	-	-	-
Nightmares	-	✔	-	-	-	-
Paresthesia	✔	-	-	✔	-	<1
Peripheral neuritis	-	-	-	✔	-	-
Psychosis	-	✔	-	✔	-	-
Seizures	✔	✔	✔	✔	-	-
Somnolence	<1	-	-	-	-	<2
Sweating	✔	-	-	-	-	<2
Syncope	✔	-	-	-	-	✔
Tinnitus	-	✔	-	✔	-	-
Tremor	-	✔	-	-	-	-
Vertigo	<1	✔	✔	✔	-	<2
Dermatological						
Desquamation	-	-	1-10	-	-	-
Dryness	-	-	1-10	-	-	-
Eczema	✔	-	-	-	-	<1
Erythema	-	-	1-10	-	-	-
Erythema multiforme	✔	-	✔	✔	-	<1
Exfoliative dermatitis	-	-	-	✔	-	-
Photosensitivity	<1	-	-	✔	-	-
Pruritus	✔	-	1-10	✔	<2	<1
Rash	<1	3	3	✔	<2	<2
Skin eruptions	-	✔	✔	✔	-	-
Stevens Johnson Syndrome	✔	✔	✔	✔	-	-
Toxic epidermal necrolysis	✔	✔	✔	✔	-	-
Urticaria	✔	✔	✔	✔	-	<1
Gastrointestinal						
Abdominal distension	-	-	-	-	<2	<2
Abdominal pain	3	2-3	8	✔	6	<2
Abdominal tenderness	-	-	-	-	<2	-
Anorexia	✔	✔	✔	✔	-	<2
Cholestatic jaundice	<1	✔	✔	-	-	-
Constipation	✔	-	-	-	-	<2
Cramping	-	-	✔	-	-	-
Diarrhea	5	3-6	7	✔	-	10
Dry mouth	-	-	-	-	-	<2
Dyspepsia	<1	2	2	-	<2	<2

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Erythromycin/ Sulfisoxazole	Fidaxomicin	Telithromycin
Dysphagia	-	-	-	-	<2	-
Flatulence	<1	-	2	✔	<2	<2
Gastritis	✔	-	-	-	-	<2
Gastroenteritis	-	-	-	-	-	<2
Gastrointestinal hemorrhage	-	-	-	✔	4	-
Gastrointestinal upset	-	-	-	-	-	<2
Glossitis	-	✔	-	✔	-	<2
Hypertrophic pyloric stenosis	-	-	✔	-	-	-
Intestinal Obstruction	-	-	-	-	<2	-
Loose stools	5-11.6	-	-	-	-	2
Megacolon	-	-	-	-	<2	-
Melena	<1	-	-	✔	-	-
Mucositis	<1	-	-	-	-	-
Nausea	3-5	3	8	✔	11	7
Oral candidiasis	✔	✔	✔	-	-	<2
Pancreatitis	✔	✔	✔	✔	-	✔
Pseudomembranous colitis	✔	-	✔	✔	-	-
Salivary gland enlargement	-	-	-	✔	-	-
Stomatitis	-	✔	-	✔	-	<2
Taste perversion	✔	3-7	1	-	-	1
Tongue discoloration	✔	✔	-	-	-	-
Tooth discoloration	-	✔	-	-	-	-
Vomiting	<2	6	3	✔	7	2
Watery stools	-	-	-	-	-	<2
Genitourinary						
Acute renal failure	✔	-	-	✔	-	-
Crystalluria	-	-	-	✔	-	-
Hematuria	-	-	-	✔	-	-
Interstitial nephritis	✔	✔	-	-	-	-
Monilia	<1	-	-	-	-	-
Nephritis	<1	-	-	✔	-	-
Toxic nephrosis with anuria	-	-	-	✔	-	-
Toxic nephrosis with oliguria	-	-	-	✔	-	-
Urinary retention	-	-	-	✔	-	-
Vaginal candidiasis	-	-	-	-	-	<2
Vaginitis	<1	-	-	-	-	-
Hematological						

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Erythromycin/ Sulfisoxazole	Fidaxomicin	Telithromycin
Agranulocytosis	-	-	-	✔	-	-
Anemia	✔	-	-	✔	2	-
Aplastic anemia	-	-	-	✔	-	-
Eosinophilia	-	-	1	✔	-	<1
Hemolytic anemia	-	-	-	✔	-	-
Leukopenia	<1	✔	-	✔	-	-
Methemoglobinemia	-	-	-	✔	-	-
Neutropenia	<1	✔	-	-	2	-
Sulfhemoglobinemia	-	-	-	✔	-	-
Thrombocytopenia	<1	✔	-	✔	<2	-
Thrombocytosis	-	-	-	-	-	<2
Hepatic						
Hepatic dysfunction	-	-	✔	-	-	✔
Hepatic failure	✔	✔	-	-	-	✔
Hepatic necrosis	✔	-	-	-	-	✔
Hepatitis	✔	✔	✔	✔	-	<1
Hepatocellular necrosis	-	-	-	✔	-	-
Hepatotoxicity	-	-	-	-	-	✔
Jaundice	✔	-	✔	✔	-	-
Laboratory Test Abnormalities						
Alkaline phosphatase increased	-	<1	-	-	<2	-
Bicarbonate decreased	-	-	-	-	<2	-
Bilirubin increased	<1	-	-	-	-	<1
BUN increased	<1	4	-	-	-	-
CPK increased	1-2	-	-	-	-	-
Creatinine increased	<1	<1	-	-	-	-
GGT increased	1-2	<1	-	-	-	-
Hepatic enzymes increased	-	-	-	-	<2	-
Hyperglycemia	<1	-	-	-	<2	-
Hyperkalemia	1-2	-	-	-	-	-
Hypofibrinogenemia	-	-	-	✔	-	-
Hypoglycemia	-	✔	-	✔	-	-
Hypoprothrombinemia	-	-	-	✔	-	-
Lactic dehydrogenase increased	<1	<1	-	-	-	-
Metabolic acidosis	-	-	-	-	<2	-
Phosphate increased	<1	-	-	-	-	-
Prothrombin time increased	-	1	-	-	-	-

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Erythromycin/ Sulfisoxazole	Fidaxomicin	Telithromycin
SGOT increased	1-2	<1	2	-	-	<2
SGPT increased	1-2	<1	2	-	-	<2
Musculoskeletal						
Arthralgia	✔	-	-	-	-	✔
Muscle cramps	-	-	-	-	-	✔
Myalgia	-	-	-	-	-	✔
Myasthenia gravis exacerbation	-	-	-	-	-	✔
Rigors	-	-	-	✔	-	-
Weakness	-	-	2	✔	-	-
Respiratory						
Bronchospasm	<1	-	-	-	-	-
Cough	✔	-	3	✔	-	-
Dyspnea	-	-	1	-	-	-
Pharyngitis	✔	-	-	-	-	-
Pneumonitis	-	-	-	✔	-	-
Pulmonary infiltrates	-	-	-	✔	-	-
Rhinitis	✔	-	-	-	-	-
Shortness of breath	-	-	-	✔	-	-
Other						
Allergic reactions	-	-	✔	-	-	-
Anaphylaxis	✔	✔	✔	✔	-	✔
Angioedema	<1	-	-	✔	-	✔
Arteritis	-	-	-	✔	-	-
Blurred vision	-	-	-	-	-	<2
Conjunctival injection	-	-	-	✔	-	-
Deafness	✔	-	-	-	-	-
Diplopia	-	-	-	-	-	<2
Diuresis	-	-	-	✔	-	-
Edema	✔	-	-	-	-	-
Facial edema	-	-	-	-	-	✔
Fatigue	<1	-	-	✔	-	<2
Flushing	-	-	-	✔	-	<1
Goiter	-	-	-	✔	-	-
Hearing disturbances	✔	-	-	-	-	-
Hearing loss	-	✔	✔	✔	-	-
Hypersensitivity reactions	-	-	✔	-	-	-
Malaise	✔	-	-	-	-	-

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Erythromycin/ Sulfisoxazole	Fidaxomicin	Telithromycin
Olfactory perversion	-	✔	-	-	-	-
Pain	✔	-	2	-	-	-
Periarteritis nodosa	-	-	-	✔	-	-
Phlebitis	-	-	✔	-	-	-
Scleral injection	-	-	-	✔	-	-
Serum sickness-like reaction	-	-	-	✔	-	-
Systemic lupus erythematosus	-	-	-	✔	-	-
Thrombophlebitis	-	-	✔	-	-	-
Tinnitus	✔	-	-	-	-	-
Vasculitis	-	-	-	✔	-	-

✔ Percent not specified
- Event not reported

Table 8. Boxed Warning for Telithromycin[1]

WARNING
Telithromycin is contraindicated in patients with myasthenia gravis. There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of telithromycin.

VII. Dosing and Administration

The usual dosing regimens for the macrolides are listed in Table 9.

Table 9. Usual Dosing Regimens for the Macrolides[1-13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Azithromycin	Acute Exacerbations of Chronic Bronchitis: Suspension (IR)/tablet (250 mg, 500 mg): 500 mg once daily for 3 days or 500 mg as a single dose on day 1, followed by 250 mg once daily on days 2-5 Chancroid: Suspension (IR)/tablet (250 mg, 500 mg): 1 g as a single dose Disseminated MAC Infections Tablet (600 mg): Prevention: 1,200 mg once weekly Treatment: 600 mg daily Gonococcal Infections (Urethritis/Cervicitis): Suspension (IR)/tablet (250 mg, 500 mg): 2 g as a single dose Nongonococcal Infections (Urethritis/Cervicitis): Suspension (IR)/tablet (250 mg, 500 mg): 1 g as a single dose Suspension (1 g): 1 g as a single dose Pelvic Inflammatory Disease: Injection: 500 mg as a single daily dose for 1 to 2 days Pharyngitis and/or Tonsillitis: Suspension (IR)/tablet (250 mg, 500 mg): 500 mg as a single dose on day 1, followed by 250 mg once daily on days 2-5 Pneumonia (Community-Acquired):	Otitis Media: ≥6 months of age: Suspension (IR)/tablet (250 mg, 500 mg): 30 mg/kg given as a single dose or 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on the first day, followed by 5 mg/kg/day on days 2 through 5 Pharyngitis and/or Tonsillitis: ≥2 years of age: Suspension (IR)/tablet (250 mg, 500 mg): 12 mg/kg once daily for 5 days Pneumonia (Community-Acquired): ≥6 months of age: Suspension (IR)/tablet (250 mg, 500 mg): 10 mg/kg on day 1, followed by 5 mg/kg on days 2-5 Suspension (ER): 60 mg/kg as a single dose Sinusitis: ≥6 months of age: Suspension (IR)/tablet (250 mg, 500 mg): 10 mg/kg once daily for 3 days	Injection: 500 mg Packet: 1 g Suspension (ER): 2 g/60 ml Suspension (IR): 100 mg/5 ml 200 mg/5 ml Tablet: 250 mg 500 mg 600 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Injection: 500 mg as a single daily dose for at least two days Suspension (ER): 2 g as a single dose Suspension (IR)/tablet (250 mg, 500 mg): 500 mg as a single dose on day 1, followed by 250 mg once daily on days 2-5 Sinusitis: Suspension (ER): 2 g as a single dose Suspension (IR)/tablet (250 mg, 500 mg): 500 mg once daily for 3 days Skin and Skin-Structure Infections: Suspension (IR)/tablet (250 mg, 500 mg): 500 mg as a single dose on day 1, followed by 250 mg once daily on days 2-5		
Clarithromycin	Acute Exacerbations of Chronic Bronchitis: Tablet (ER):1,000 mg once daily for 7 days Tablet (IR): *H influenzae* and *H parainfluenzae*: 500 mg every 12 hours for 7-14 days *M catarrhalis* and *S pneumoniae*: 250 mg every 12 hours for 7-14 days Disseminated MAC Infections Tablet (IR): Prevention: 500 mg every 12 hours Treatment: 500 mg every 12 hours *H pylori* Eradication: Triple therapy: Tablet (IR): 500 mg every 12 hours for 10-14 days given with amoxicillin and either lansoprazole or omeprazole Dual therapy: Tablet (IR): 500 mg every 8 to	Disseminated MAC Infections ≥6 months: Prevention: 7.5 mg/kg orally every 12 hours, up to 500 mg every 12 hours Treatment: 7.5 mg/kg orally every 12 hours, up to 500 mg every 12 hours Otitis Media: ≥6 months: Suspension/tablet (IR): 15 mg/kg/day divided every 12 hours for 10 days Pharyngitis and/or Tonsillitis: ≥6 months: Suspension/tablet (IR): 15 mg/kg/day divided every 12 hours for 10 days Pneumonia (Community-Acquired): ≥6 months: Suspension/tablet (IR): 15 mg/kg/day divided every 12 hours for 10 days Sinusitis: ≥6 months:	Suspension: 125 mg/5 ml 250 mg/5 ml Tablet (ER): 500 mg Tablet (IR): 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	12 hours for 14 days given with ranitidine bismuth citrate or omeprazole Pharyngitis and/or Tonsillitis: Tablet (IR): 250 mg every 12 hours for 10 days Pneumonia (Community-Acquired): Tablet (ER):1,000 mg once daily for 7 days Tablet (IR): 250 mg every 12 hours for 7-14 days Sinusitis: Tablet (ER): 1,000 mg once daily for 14 days Tablet (IR): 500 mg every 12 hours for 14 days Skin and Skin-Structure Infections: Tablet (IR): 250 mg every 12 hours for 7-14 days	Suspension/tablet (IR): 15 mg/kg/day divided every 12 hours for 10 days Skin and Skin-Structure Infections: ≥6 months: Suspension/tablet (IR): 15 mg/kg/day divided every 12 hours for 10 days	
Erythromycin base	Intestinal Amebiasis: 500 mg every 12 hours or 250 mg every 6 hours for 10-14 days Legionnaires' Disease: 1-4 g daily in divided doses Nongonococcal Urethritis: 500 mg 4 times daily for 7 days Pelvic Inflammatory Disease: 500 mg IV every 6 hours for 3 days followed by 500 mg orally every 12 hours for 7 days Pertussis: 40-50 mg/kg/day in divided doses for 5-14 days Pharyngitis and/or Tonsillitis: 250 mg 4 times daily or 500 mg every 12 hours for 10 days Pneumonia of Infancy: 50 mg/kg/day in 4 divided doses for at least 3 weeks (suspension) Syphilis: 30-40 grams given in divided	Conjunctivitis of the Newborn: 50 mg/kg/day in 4 divided doses for at least 2 weeks (suspension) Intestinal Amebiasis: 30-50 mg/kg/day in divided doses for 10-14 days Unspecified Infections: 30-50 mg/kg/day in 2-4 divided doses	Capsule (DR): 250 mg Tablet: 250 mg 500 mg Tablet (coated-particle): 333 mg 500 mg Tablet (DR): 250 mg 333 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	doses over 10-15 days Unspecified Infections: 250 mg 4 times daily or 500 mg every 12 hours Urogenital Infections in Pregnancy: 500 mg 4 times daily for 7 days or either 250 mg 4 times daily or 500 mg every 12 hours for 14 days		
Erythromycin ethylsuccinate	Intestinal Amebiasis: 400 mg 4 times daily for 10-14 days Legionnaires' Disease: 1.6-4 g daily in divided doses Pertussis: 40-50 mg/kg/day in divided doses for 5-14 days Syphilis: 48-64 g in divided doses over 10-15 days Unspecified Infections: 400 mg every 6 hours, or total daily dose divided every 8 or every 12 hours Urethritis: 800 mg 3 times daily for 7 days	Intestinal Amebiasis: 30-50 mg/kg/day in divided doses for 10-14 days Unspecified Infections: 30-50 mg/kg/day in 2-4 divided doses	Suspension: 200 mg/5 ml 400 mg/5 ml Tablet: 400 mg
Erythromycin ethylsuccinate and sulfisoxazole	Unspecified Infections: 400 mg of the erythromycin component and 1,200 mg of the sulfisoxazole component every 6 hours	Unspecified Infections: ≥2 months of age: 50 mg/kg/day (based on erythromycin component) divided in 3-4 doses for 10 days or 150 mg/kg/day (based on the sulfisoxazole component) divided in 3-4 doses for 10 days	Suspension: 200-600 mg/5 ml
Erythromycin lactobionate	Unspecified Infections: 15-20 mg/kg/day every 6 hours or 0.5 to 1 g every 6 hours or continuous infusion	Unspecified Infections: 15-20 mg/kg/day divided every 6 hours	Injection: 500 mg 1 g
Erythromycin stearate	Unspecified Infections: 250 mg every 6 hours or 500 mg every 12 hours up to 4 g per day	Unspecified Infections: 30-50 mg/kg/day in 2-4 divided doses	Tablet: 250 mg
Fidaxomicin	*Clostridium difficile*-Associated Diarrhea: 200 mg twice daily for 10 days	Safety and efficacy in children has not been established.	Tablet: 200 mg
Telithromycin	Pneumonia (Community-Acquired): 800 mg once daily for 7-10 days	Safety and efficacy in children has not been established.	Tablet: 300 mg 400 mg

DR=delayed-release, IR=immediate-release, XR=extended-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the macrolides are summarized in Table 10.

Table 10. Comparative Clinical Trials with the Macrolides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Montero[67] (1996) Azithromycin 10 mg/kg daily for 3 days vs cefaclor 20 mg/kg/day in 3 divided doses for 10 days	MC, RCT, OL Patients 6 months to 12 years of age with skin and/or soft tissue infections	N=200 10 days	Primary: Clinical response, bacteriologic response	Primary: The clinical efficacy was comparable between treatment groups (94% in the azithromycin group and 95% in the cefaclor group). In the azithromycin group, 95% of pathogens were eradicated and 99% of pathogens were eradicated in the cefaclor group.
Amaya-Tapia et al.[68] (1993) Azithromycin 500 mg daily for 3 days vs dicloxacillin 250 mg QID for 7 days	RCT, PRO, SB Adult patients with skin and skin structure infections	N=62 7 days	Primary: Clinical response, bacteriologic response	Primary: Clinical resolution was observed in 83.3% of patients in the azithromycin group and 83.9% in the dicloxacillin group. No significant difference was found between groups. Bacteriologic eradication was observed in 90.0% of patients in the azithromycin group compared to 87.1% in the dicloxacillin group. No significant difference was found between groups.
Wasilewski et al.[69] (2000) Dirithromycin 500 mg daily for 5	RCT, DB, DD, MC, PG Patients 12 years of age or older with a	N=439 Treatment duration plus 10-14 days	Primary: Clinical response (cure defined as resolution of pre-treatment signs and	Primary: A favorable response was seen in 85.0% of patients in the dirithromycin group compared to 80.8% of patients in the erythromycin group. No significant differences were observed.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days vs erythromycin 250 mg every 6 hours for 7 days	culturable bacterial infection of the skin and/or soft tissue		symptoms), bacteriologic response (eradication of pathogen based on culture results)	A favorable bacteriologic response was seen in 66.4% of patients in the dirithromycin group and 63.5% in the erythromycin group. No significant differences were observed.
Gastrointestinal Infections				
Kaushik et al.[107] (2010) Azithromycin 20 mg/kg as a single dose vs ciprofloxacin 20 mg/kg as a single dose	RCT, OL Children 2 to 12 years of age with watery diarrhea for ≤24 hours and severe dehydration, who tested positive for *Vibrio cholerae* by hanging drop examination or culture of stool	N=180 3 days	Primary: Clinical success (resolution of diarrhea within 24 hours) and bacteriological success (cessation of excretion of *Vibrio cholerae* by day 3) Secondary: Duration of diarrhea, duration of excretion of *Vibrio cholerae* in stool, fluid requirement, and proportion of children with clinical or bacteriological relapse	Primary: Clinical success was 94.5% with azithromycin compared to 70.7% with ciprofloxacin (RR 1.34; 95% CI, 1.16 to 1.54; P<0.001). Bacteriological success was 100% with azithromycin compared to 95.5% with ciprofloxacin (RR 1.05; 95% CI, 1.00 to 1.10; P=0.06). Secondary: Patients treated with azithromycin had a shorter duration of diarrhea compared to patients receiving ciprofloxacin (54.6 hours vs 71.5 hours, respectively; P<0.001). Patients receiving azithromycin had a lesser duration of excretion of *Vibrio cholerae* than patients receiving ciprofloxacin (34.6 hours vs 52.1 hours; P<0.001). The amount of intravenous fluid was significantly less among patients who received azithromycin compared to those who received ciprofloxacin (4,704.7 ml vs 3,491.1 ml); P<0.001). The proportion of children with bacteriological relapse was comparable in both groups (6.7% with azithromycin vs 2.2% with ciprofloxacin; P=0.16). None of the children in either group had a clinical relapse.
Vukelic et al.[101] (2010) Azithromycin 20	RCT, SC Children ≤12 years of age with *C.*	N=120 Variable duration	Primary: Clinical cure rates achieved during the 144 hours	Primary: The incidence of clinically cured patients during the 144-hour study period was 50% in the control, 46.6% in the azithromycin 20 mg/kg group, 66.6% in the azithromycin 30 mg/kg group, and 83.3% in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg as a single oral dose vs azithromycin 30 mg/kg as a single oral dose vs erythromycin 50 mg/kg/day orally divided in 3 daily doses for 5 days vs no antibiotic (control group)	*jejuni/coli* enterocolitis		study period and safety	erythromycin group. Only azithromycin 30 mg/kg was significantly more effective than no treatment (P=0.011). Azithromycin 30mg/kg was also significantly more effective than erythromycin (P=0.006). There was no difference between the erythromycin and the control group. All treatments were well tolerated.
Mantzaris et al.[48] (2002) Clarithromycin 500 mg BID, amoxicillin 1g BID, and omeprazole 20 mg BID for 10 days (OAC) vs omeprazole 20 mg BID, colloidal bismuth subcitrate 120 mg QID,	RCT, SB Patients 16-70 years of age with an active duodenal ulcer	N=149 24 months	Primary: Endoscopic healing rates, eradication of *H pylori* 10-12 weeks after therapy Secondary: Influence of demographic and clinical parameters on eradication rates, relapse of *H pylori* infection and duodenal ulcer after 12 and 24 months, and development of	Primary: There were no significant differences in ulcer healing rates between the two treatment groups (P>0.8). There were no significant differences in eradication rates between the two treatment groups (P>0.1). Secondary: There were no demographic or clinical parameters which effected the eradication rates in either group (P>0.08). There were no significant differences in any other secondary endpoint between groups. The annual relapse rate of *H pylori* was reported as 3%. The relapse rate at 24 months was reported as 5%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metronidazole 500 mg TID, and tetracycline 500 mg QID for 10 days (OBMT)			post-eradication reflux esophagitis	
Molina-Infante et al.[108] (2010) Clarithromycin 500 mg, omeprazole 20 mg, and amoxicillin 1g TID (OCA) vs levofloxacin 500 mg, omeprazole 20 mg, and amoxicillin 1g TID (OLA) vs omeprazole 20 mg and amoxicillin 1g BID for 5 days, followed by omeprazole 10 mg, clarithromycin 500 mg, and metronidazole TID for 5 days (OACM)	RCT, OL Patients >18 years of age with *Helicobacter pylori* infection, determined by a positive urea breath test, histology, or rapid urease test	N=460 10 days	Primary: Eradication of *Helicobacter pylori* infection Secondary: Tolerance and compliance	Primary: The PP cure rates were 66% with OCA (95% CI, 57% to 74%), 82.4% with OLA (95% CI, 75% to 89%; P<0.05 vs OCA), 80.8% with OACM (95% CI, 73% to 88%; P<0.05 vs OCA), and 82.5% with OALM (95% CI, 78-91%; P<0.05 vs OCA). The ITT cure rates were 64% with OCA (95% CI, 55% to 73%), 80.8% with OLA (95% CI, 73% to 88%; P<0.05 vs OCA), 76.5% with OACM (95% CI, 69% to 85%; P<0.05 vs OCA), and 82.5% with OALM (95% CI, 75% to 89%; P<0.05 vs OCA). Secondary: No differences in adverse effects or compliance were demonstrated among treatments by questionnaire assessment. Minor or mild side effects were reported by 28% of patients without significant differences between treatments. No major adverse events were observed, though 9 patients discontinued therapy reportedly due to adverse events. A total of 97% of patients had complete adherence to antibiotic therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs omeprazole 20 mg and amoxicillin 1g BID for 5 days, followed by omeprazole 20 mg, levofloxacin 500 mg, and metronidazole 500 mg TID for 5 days (OALM)				
Ohlin et al.[49] (2002) Clarithromycin 500 mg BID, amoxicillin 1g BID, and lansoprazole 30 mg BID for 14 days (LAC) vs lansoprazole 30 mg BID and amoxicillin 1g BID for 14 days (LA) vs omeprazole 20 mg BID and amoxicillin 1g	RCT, DB, MC Patients 18-80 years of age with *H pylori* infection and a present recurrent duodenal ulcer and/or previous recurrent duodenal ulcer	N=177 4 weeks posttreatment	Primary: Eradication of *H pylori* at least 4 weeks after the end of treatment period	Primary: Triple therapy with LAC was significantly better than either dual therapy with OA or LA in ulcer healing and eradication of *H pylori* (P<0.001). There was no significant difference between dual therapy groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID for 14 days (OA)				
Uygun et al.[93] (2007) Clarithromycin 500 mg BID, lansoprazole 30 mg BID and amoxicillin 1 g BID (LAC) vs bismuth subsalicylate 300 mg QID, lansoprazole 30 mg BID, tetracycline 500 mg QID. and metronidazole 500 mg TID (BLTM)	RCT, SC, SB *H. pylori*-positive patients with non-ulcer dyspepsia	N=240 14 days	Primary: *H. pylori* eradication rates and safety	Primary: In the ITT and PP populations, *H. pylori* eradication rates were 70% (95% CI, 61–78) and 82.3% (95% CI, 74–89) in the BLTM group, and 57.5% (95% CI, 48–66) and 62.7% (95% CI 53–71) in the LAC group. The BLTM treatment achieved a significantly better eradication rate than the LAC treatment in PP analysis (82.3% vs 62.7%, P=0.002). Although a better ITT rate was obtained in the BLTM group than in the LAC group, the difference was not significant (70% vs 57.5%, P=0.06). Mild to severe adverse events, which were more frequent in the BLTM group, were reported in 18.2% of the patients. Although it was not significant, the number of patients ceasing the treatment for adverse events was higher in BLTM group than in the LAC group.
Louie et al.[106] (2011) Fidaxomicin 200 mg twice daily for 10 days vs vancomycin 125 mg orally four times daily for 10 days	MC, DB, RCT Patients ≥16 years of age with diarrhea and a diagnosis of *C. difficile* infection, as well as the presence of *C. difficile* toxin A, B, or both in the stool	N=629 28 days posttreatment	Primary: Clinical cure (resolution of symptoms and no need for further therapy for *C. difficile* infection as of the second day after the end of the course of therapy) Secondary: Recurrence of *C.*	Primary: Clinical cure rates in the modified ITT analysis were 88.2% with fidaxomicin and 85.8% with vancomycin. Clinical cure rates in the PP analysis were 92.1% for fidaxomicin and 89.8% for vancomycin. The rates of clinical cure with fidaxomicin were non-inferior to those with vancomycin. Secondary: Recurrence in the modified ITT analysis was 15.4% with fidaxomicin compared to 25.3% with vancomycin (P=0.005). Recurrence in the PP analysis was 13.3% with fidaxomicin compared to 24% with vancomycin (P=0.004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			difficile infection (diarrhea and a positive result on a stool toxin test within 4 weeks after treatment)	Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection.
Genitourinary Infections				
Martin et al.[45] (1995) Azithromycin 1 g as a single dose vs ceftriaxone 250 mg IM as a single dose	RCT, MC Patients ≥16 years of age with a painful genital ulcer, negative darkfield examination, and a negative syphilis reagin test (unless a previous history of syphilis)	N=197 19 to 23 days	Primary: Response to treatment (healed, improved, not improved)	Primary: Complete healing was documented in 66% of azithromycin patients and 52% of the ceftriaxone patients at the first visit (6-8 days after treatment, P>0.05). By the third follow-up visit, 100% of patients in the azithromycin group were completely healed compared to 88% of the ceftriaxone patients (P>0.05). The remaining 4 patients in the ceftriaxone group at visit 3 were judged as clinically improved.
Tyndall et al.[44] (1994) Azithromycin 1 g as a single dose vs erythromycin 500 mg QID or 7 days	RCT, SB Male patients 18-60 years of age with genital ulcers	N=204 21 days	Primary: Response to treatment (cure defined as epithelialization of ulcer complete by day 21)	Primary: Complete ulcer resolution was observed in 89% of men in the azithromycin group and 91% of men in the erythromycin group.
Hook et al.[70] (2002) Azithromycin 2 g as a single dose vs	RCT Patients 18-56 years of age with early syphilis	N=74 12 months	Primary: Therapeutic response	Primary: The overall response rate for patients in the benzathine penicillin G group was 86%. The overall response rate for patients in the single-dose azithromycin group was 94%, which was not significantly different from the penicillin group (P=0.75).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
azithromycin 2 g as 2 doses given 6 to 8 days apart vs penicillin benzathine G 2.4 million units IM as a single dose				The overall response rate for patients in the double-dose azithromycin group was 83% and was not significantly different from the penicillin group (P=0.95).
Hook et al.[97] (2010) Azithromycin 2 g as a single dose vs penicillin benzathine G 2.4 million units IM as a single dose	RCT, MC, OL Patients 18 to 55 years of age with early syphilis (primary, secondary, or early latent)	N=517 6 months	Primary: Serological cure of infection	Primary: In the ITT analysis at the 6-month follow-up visit, 77.6% of azithromycin patients and 78.5% of penicillin patients experienced serological cure (1-sided lower bound of the 95% CI of the difference, −7.2%). In the PP analysis at the 6-month follow-up visit, 77.5%) of azithromycin patients and 78.9%) of penicillin patients experienced serological cure (1-sided 95% CI lower bound was −7.9%). The efficacy of 2 grams azithromycin administered orally was non-inferior to the administration of benzathine penicillin G for the treatment of early syphilis in patients without HIV infection.
Riedner et al.[71] (2005) Azithromycin 2 g as a single dose vs penicillin benzathine G 2.4 million units IM as a single dose	RCT Patients 15-60 years of age with confirmed early syphilis (primary or secondary) or high-titer latent syphilis	N=328 9 months	Primary: Serologic cure at 9 months Secondary: Serologic cure rates 3 and 6 months after treatment, cure rates according to age, sex, stage of syphilis, and plasma regain (PR) titer at treatment	Primary: After 9 months, cure rates were 97.7% in the azithromycin group and 95.0% in the penicillin group. There was no significant difference between the treatment groups (P=0.23). Secondary: Cure rates at 3 months were 59.4% in the azithromycin group and 59.5% in the penicillin group. There was no significant difference between the treatment groups. Cure rates at 6 months were 85.5% in the azithromycin group and 81.5% in the penicillin group. There was no significant difference between the treatment groups. There were no significant differences between groups in cure rates

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				according to age, sex, stage of syphilis, and PR titer at treatment (P>0.33).
Bai et al.[84] (2008) Azithromycin vs penicillin G benzathine	MA Patients ≥18 years of age with early syphilis	N=476 (4 trials) Variable duration	Primary: Cure rates and adverse events	Primary: In the azithromycin group, serology cure occurred in 95% of patients. In the penicillin G benzathine group, serology cure occurred in 84.0% of patients (OR, 1.37; 95% CI, 1.05 to 1.77; P=0.02). The pooled OR for primary syphilis with the administration of azithromycin as compared to penicillin G benzathine was 0.69 (95% CI, 0.09 to 1.61; P=0.38). There was no significant difference in the rate of adverse events between the treatment groups.
Martin et al.[74] (1992) Azithromycin 1 g as a single dose vs doxycycline 100 mg BID for 7 days	RCT, OL Patients 16 to 50 years of age with presumptive chlamydial urethral or endocervical infections	N=457 35 days	Primary: Clinical response	Primary: At the last follow-up visit, 97% of males and 98% of females in the azithromycin group had clinically responded to treatment and 91% of males and 95% of females in the doxycycline group had responded to treatment. No significant differences between groups were identified. There were no significant differences in bacteriologic cure rates between the treatment groups at any time.
Lauharanta et al.[75] (1993) Azithromycin 1 g as a single dose vs doxycycline 100 mg BID for 7 days	RCT, PRO, OL Patients 18-60 years of age with signs and symptoms of non-gonococcal urethritis	N=120 35 days	Primary: Clinical response and eradication rate	Primary: There was no significant difference in clinical response or eradication rates between groups at any time, except at visit 3 (35 days), when there was a significantly higher cure rate in the azithromycin group compared to the doxycycline group in *Chlamydia*-negative patients (79% and 35% respectively, P=0.017).
Lister et al.[76] (1993) Azithromycin 1 g as a single dose	OL, CS Men 19-57 years of age with symptoms and/or signs of non-	N=143 21 days	Primary: Clinical cure, cure on microscopy, and microbiological cure (eradication of	Primary: No significant differences were seen between treatment groups in any primary outcome measure.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs doxycycline 100 mg BID for 7 days	gonococcal urethritis (NGU) and 5 or more polymorphonuclear leucocytes		*C trachomatis* from the urethra)	
Mena et al.[98] (2009) Azithromycin 1 gram as a single dose vs doxycycline 100 mg BID for 7 days	RCT, SC Men with signs or symptoms of urethral disease who met clinical criteria for nongonococcal urethritis	N=398 6 weeks	Primary: Persistence or recurrence of *M. genitalium* infection	Primary: From the initial study population enrolled, 36 men in the azithromycin group and 42 men in the doxycycline group tested positive at the initial study enrollment for *M. genitalium*. Of those testing positive at initial follow-up (10-17 days post therapy), 13% (95% CI, 3 to 35) were from the azithromycin group compared to 55% in the doxycycline group (95% CI, 36 to 72; P=0.002). Of the 15 persistently *M. genitalium* infected men who were clinically cured at the early initial follow-up visit, 47% experienced clinical relapse over the subsequent 2-6 weeks.
Adair et al.[79] (1998) Azithromycin 1 g as a single dose vs erythromycin 500 mg every 6 hours for 7 days	RCT, OL Pregnant females with positive deoxyribonucleic acid (DNA) antigen assays for *Chlamydia trachomatis*	N=106 3 weeks posttreatment	Primary: Response to therapy (eradication determined by DNA assay probe)	Primary: There was no significant difference in treatment efficacy between groups (88.1% compared to 93.0% for azithromycin and erythromycin respectively, P>0.05).
Bevan et al.[53] (2003) Azithromycin 500 mg IV once daily for 1 to 2 days, followed by 250 mg orally once daily for 7 days (group A)	MA, OL, MC, CS Women 18 years of age or older with a clinical diagnosis of acute pelvic inflammatory disease (PID) requiring hospitalization	N=310 44 days	Primary: Response to treatment	Primary: Clinical success (cure or improvement) was reported in 97.1% of patients in group A, 98.1% in group B, and 94.6% of patients in group C. There was no significant difference between groups. Eradication was reported in 97.6% of patients in group A, 95.5% of patients in group B, and 97.0% of patients in group C. There was no significant difference between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs azithromycin 500 mg IV once daily for 1 to 2 days, followed by 250 mg orally once daily for 7 days plus metronidazole 400 to 500 mg IV TID, followed by oral therapy for a total of 12-14 days (group B) vs metronidazole plus doxycycline plus cefoxitin plus probenecid or doxycycline plus amoxicillin-clavulanate at standard doses (group C)				
Savaris et al.[87] (2007) Azithromycin 1 g per week plus ceftriaxone 250 mg IM injection vs	RCT Patients with mild pelvic inflammatory disease (PID)	N=133 2 weeks	Primary: Clinical cure	Primary: Clinical cure in the PP analysis was 98.2% (95% CI, 0.9-0.99) with azithromycin and 85.7% (95% CI, 0.72-0.93) with doxycycline (P=0.02). In the modified ITT analysis, clinical cure was 90.3% (95% CI, 0.80-0.96) with azithromycin and 72.4% (95% CI, 0.58-0.82) with doxycycline (P=0.01). No significant difference was observed regarding the degree of pain

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doxycycline 200 mg per day plus ceftriaxone 250 mg IM injection				between the doxycycline and azithromycin groups.
Mikamo et al.[77] (1999) Clarithromycin 400 mg BID for 5, 7, or 14 days (CAM) vs erythromycin 600 mg TID for 5, 7, or 14 days (EM)	RCT Female patients 17-56 years of age with cervicitis caused by *C trachomatis*	N=96 6 weeks	Primary: Eradication of *C trachomatis*	Primary: Eradication rates were significantly higher in the 7-day CAM group compared to the 7-day EM group. Eradication rates were significantly higher in the 14-day CAM group compared to the 14-day EM group.
Moller et al.[78] (1990) Erythromycin 500 mg BID for 7 days vs ofloxacin 200 mg BID for 7 days	RCT, DB Male patients with nongonococcal urethritis	N=188 15 days	Primary: Clinical response (cure defined as resolution of signs and symptoms of infection)	Primary: At day 15, there was no significant difference in clinical response seen between groups (77.4% in the erythromycin group and 84.3% in the ofloxacin group).
Respiratory Infections				
Pichichero et al.[54] (2003) Azithromycin 10 mg/kg on day 1, followed by 5 mg/kg on days 2-5	OL Patients 6 months to 20 years of age with a diagnosis of pertussis	N=34 21 days posttreatment	Primary: Bacteriologic eradication	Primary: Microbiological eradication was observed in 97% of patients at days 2-3 of treatment and in 100% of patients at the 14-21 day post-treatment follow-up visit.
Albert et al.[100]	RCT, PC, MC	N=1,142	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) Azithromycin 250 mg daily for 1 year vs placebo	Patients ≥40 years of age with COPD who were either using continuous supplemental oxygen or had received systemic glucocorticoids within the previous year, who had gone to an emergency room or had been hospitalized for an acute exacerbation of COPD, who had not had an acute exacerbation of COPD for at least 4 weeks before enrollment	13 months	Time to the first acute exacerbation of COPD Secondary: Quality of life and adherence	The median time to the first exacerbation of COPD was 266 days (95% CI, 227 to 313) with azithromycin compared to 174 days (95% CI, 143 to 215) with placebo (P<0.001). The hazard ratio of having an acute exacerbation of COPD per patient-year in the azithromycin group as compared with the placebo group was 0.73 (95% CI, 0.63 to 0.84; P<0.001). The rates of acute exacerbations of COPD per patient-year were 1.48 with azithromycin and 1.83 with placebo (P=0.01). The frequency of acute exacerbations was lower among patients receiving azithromycin than among those receiving placebo (P=0.008). Secondary: The total SGRQ scores recorded at 1 year decreased a mean of 2.8 units in the azithromycin group compared with a mean of 0.6 units in the placebo group (P=0.004). No consistent changes were seen in the scores on the SF-36. The mean rate of adherence to the study medication was 67.3% in the azithromycin group and 66.9% in the placebo group (P=0.84).
Jorgensen et al.[104] (2009) Azithromycin extended-release 2 g as a single dose (AZ-ER) vs azithromycin immediate release 500 mg once daily for 3 days (AZ-IR)	RCT, DB, MC Patients ≥13 years of age with group A β-hemolytic streptococcal pharyngitis or tonsillitis	N=598 Up to 45 days	Primary: Bacteriological response at the test-of-cure (TOC) visit (days 24-28) in the bacteriological protocol (BPP) population Secondary: Clinical cure rates at the TOC visit and long-term follow-up (LTFU)	Primary: Bacteriological eradication was achieved in 85.4% of the patients receiving AZ-ER and in 81.4% of patients receiving AZ-IR (95% CI, -3.1 to 11.1). Secondary: Clinical cure at the TOC visit was 99% in the AZ-ER group and 96.7% in the AZ-IR group. The continued clinical cure rates at LTFU were 92.1% and 95.2% for patients in the AZ-ER and AZ-IR treatment groups, respectively. One hundred percent of patients in the AZ-ER group and 98% in the AZ-IR group complied with active treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			visit (days 38-45)	
Morris et al.[102] (2010) Azithromycin 30 mg/kg as a single dose vs amoxicillin 50 mg/kg/day in two divided doses for a minimum of 7 days	RCT, SB Aboriginal children 6 months to 6 years of age with acute otitis media	N=320 Up to 21 days	Primary: Clinical failure (defined as persistent ear pain, bulging tympanic membrane or middle ear discharge) at the end of therapy visit (days 6 to 11), failure to improve (defined as no improvement in clinical signs at the end of therapy at the end of therapy visit (days 6 to 11) Secondary: Clinical and microbiological outcomes	Primary: At the end of therapy, 50% of patients receiving azithromycin and 54% of patients receiving amoxicillin were clinical failures (P=0.504). At the end of therapy, 45% of patients receiving azithromycin and 49% of patients receiving amoxicillin failed to improve (P=0.567). Secondary: No differences in clinical failure or failure to improve were indicated in a per protocol analysis (children seen before day 11 after commencement of treatment). Azithromycin significantly reduced the proportion of children with nasal carriage of *S. pneumoniae* compared to amoxicillin (P<0.001).
Henry et al.[96] (2003) Azithromycin 500 mg daily for 3 days (AZM-3) vs azithromycin 500 mg daily for 6 days (AZM-6) vs	RCT, DB, DD, CS, MC Patients 18 years of age or older with acute bacterial sinusitis	N=936 28 days	Primary: Clinical success at end of study (EOS)	Primary: Cure rates were 71.7% in the AZM-3 group, 73.4% in the AZM-6 group, and 71.3% in the AMC group. There was no significant difference between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amoxicillin-clavulanate 500 mg TID for 10 days (AMC)				
Klapan et al.[34] (1999) Azithromycin 500 mg daily for 3 days vs amoxicillin-clavulanate 625 mg every 8 hours for 10 days	OL, CS, RCT Patients 15-50 years of age with sinusitis	N=100 4 weeks	Primary: Clinical response and bacteriologic response	Primary: Cure was established in 95% of patients in the azithromycin group and 74% of patients in the amoxicillin-clavulanate group at the end of therapy (day 10-12), and clinical improvement was seen in the remainder of patients in both groups (P=0.012 in favor of azithromycin). At the follow-up visit (4 weeks), cure was established in 98% of patients in the azithromycin group and 91% in the amoxicillin-clavulanate group. No significant differences were observed between groups (P>0.05). There was no significant difference in bacteriologic response seen between groups (P=0.409).
Marple et al.[99] (2010) Azithromycin extended-release 2 g as a single dose vs amoxicillin-clavulanate 875 mg/125 mg every 12 hours for 10 days	RCT, MC, OL Patients ≥18 years of age with acute, uncomplicated, bacterial maxillary sinusitis based on signs and symptoms lasting for 7 to 30 days	N=751 28 days	Primary: Symptom resolution at day 5 in the PP population Secondary: Time to resolution of symptoms, sinusitis-related quality of life, resource use, treatment success, and treatment satisfaction	Primary: At day 5 in the PP population, 29.7% of patients receiving azithromycin and 18.9% of patients receiving amoxicillin-clavulanate had symptom resolution (difference=10.8%; 95% CI, 3.1% to 18.4%). At day 5 in the ITT population, a significantly greater percentage of patients in the azithromycin group met the primary end point (20.0%) than in the amoxicillin-clavulanate group (13.2%; difference = 6.8%; 95% CI, 1.5% to 12.2%). Secondary: Over the course of the trial, both treatments led to similar rates of symptom resolution (HR, 1.16; 95% CI, 0.92 to 1.44). After 28 days, 67.4% of patients treated with azithromycin reported symptom resolution compared with 63.0% of patients receiving amoxicillin-clavulanate. There was no significant difference in mean reductions in SNOT-16 scores

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				among the treatment groups at the first telephone interview and second interview in the PP population. In the PP population, 11.2% of patients reported receiving a prescription for a second antibiotic during the study period. The proportion of patients requiring additional antibiotics was similar in the azithromycin group (11.0%) and the amoxicillin-clavulanate group (11.3%). A similar number of patients reported unscheduled physician visits during the study in both treatment arms. Overall satisfaction with treatment was similar in the 2 treatment arms. Patients treated with azithromycin reported greater satisfaction with the convenience of the medication than did patients given amoxicillin-clavulanate (difference = 11.59; 95% CI, 8.78 to 14.40). Patients in the amoxicillin-clavulanate arm reported greater satisfaction with side effects than those treated with azithromycin (difference = −4.40; 95% CI, −8.13 to −0.66). More patients treated with azithromycin reported abdominal discomfort than did those receiving amoxicillin-clavulanate (70.76% vs 60.92%; P=0.02). There was no difference in the incidence of diarrhea among the treatment groups (P=0.50).
Arguedas et al.[103] (2011) Azithromycin extended-release 60 mg/kg as a single dose vs amoxicillin-clavulanate 45/3.2 mg/kg every 12 hours for	RCT, DB, MC Patients 3 to 48 months of age with acute otitis media	N=923 28 to 64 days	Primary: Clinical response at the test-of-cure (TOC) visit (days 12-14) in the bacteriologic eligible population Secondary: Bacterial response at other visits, compliance, and safety	Primary: Clinical response at the TOC visit was achieved in 80.5% of children in the azithromycin group compared to 84.5% in the amoxicillin-clavulanate group (difference – 3.9%; 95% CI, –10.4 to 2.6). Azithromycin was found to be non-inferior to amoxicillin-clavulanate. Secondary: The eradication rate across all ages was 82.6% in the azithromycin group and 92% in the amoxicillin-clavulanate group (P=0.050). Eradication rates were similar for *H. influenzae*, *M. catarrhalis* and S. *pyogenes*. Eradication rates were lower in the azithromycin group than in the amoxicillin-clavulanate group for *S. pneumoniae* (83.3% vs 97.9%; P=0.018). All penicillin-susceptible isolates were eradicated in both groups. All 11 penicillin-resistant *S. pneumoniae* isolates in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
10 days				amoxicillin/clavulanate arm were eradicated. All patients receiving treatment with azithromycin received their single dose of active treatment; 59% of patients receiving amoxicillin-clavulanate received the full course of 20 doses. In the bacteriologic eligible population, 77% of patients in the amoxicillin-clavulanate arm were compliant with the full course of treatment compared with 100% of patients in the azithromycin group. Adverse events occurred in 56% of children treated with azithromycin ER and in 62.2% of children treated with amoxicillin-clavulanate. Most adverse events were of mild to moderate severity. Treatment-related vomiting was reported in 10.7% of patients receiving azithromycin and in 8.2% of patients receiving amoxicillin-clavulanate.
Panpanich et al.[85] (2008) Azithromycin vs amoxicillin or amoxicillin-clavulanate	MA Patients with acute lower respiratory tract infections	N=2601 (15 trials) 10-14 days	Primary: Clinical failure Secondary: Microbial eradication, and adverse events	Primary: The pooled analysis of all trials showed that the incidence of clinical failure on day 10 to 14 in azithromycin group was 10.1% compared to 10.3% in the amoxicillin or amoxicillin/clavulanate group (RR, 1.09; 95% CI 0.64 to 1.85). Subgroup analysis stratified by age groups showed no significant difference of treatment effects between the azithromycin group and the amoxycillin or amoxicillin/clavulanate group in either adults (RR, 1.15; 95% CI 0.60 to 2.20) or children (RR 0.93; 95% CI 0.45 to 1.94). Secondary: The pooled analysis showed that the incidence of microbial eradication in azithromycin group was 66.4% compared to 67.6% in amoxicillin or amoxicillin/clavulanate group. (RR, 0.95; 95% CI 0.87 to 1.03). The overall incidence of adverse events in azithromycin group was 17.9% compared to 23.6% in amoxicillin or amoxicillin/clavulanate group (RR 0.76; 95% CI 0.57 to 1.00).
Swanson et al.[38] (2005) Azithromycin 500	RCT, DB, DD, MC Patients with an acute exacerbation	N=322 24 days	Primary: Clinical response and bacteriologic response at the	Primary: No significant differences in the clinical cure rates were found between groups at the TOC visit (85% for azithromycin and 82% for clarithromycin).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg daily for 3 days vs clarithromycin 500 mg BID for 10 days	of chronic bronchitis		test-of-cure (TOC) visit (21-24 days)	No significant differences in the bacteriologic response rates were found between groups at the TOC visit.
Venuta et al.[57] (1998) Azithromycin 10 mg/kg once daily for 3 days vs clarithromycin 7.5 mg/kg BID for 10 days	RCT, SB, CS Patients 4-13 years of age diagnosed with streptococcal pharyngitis with a positive antigen test throat culture	N=174 20 days	Primary: Clinical response, bacteriologic response	Primary: Cure rates were 95.9% in the azithromycin group and 96.8% in the clarithromycin group. There was no significant difference between groups. There was no significant difference in bacteriologic eradication rates between groups.
Drehobl et al.[59] (2005) Azithromycin 2 g single dose vs clarithromycin extended-release 100 mg daily for 7 days	RCT, MC, DB Patients 16 years of age and older with a diagnosis of pneumonia and suitable for outpatient treatment	N=499 35 days	Primary: Clinical response at the test-of-cure (TOC) visit (day 14-21), bacteriologic response	Primary: The clinical response at the TOC visit was 92.6% in the azithromycin group and 94.7% in the clarithromycin group. No significant difference was found between groups. Bacteriologic eradication occurred in 91.8% of azithromycin patients and 90.5% of clarithromycin patients, although most bacteriologic responded were based on clinical response rather than follow-up cultures. No significant differences were seen between groups.
O'Doherty et al. [64] (1998) Azithromycin 500 mg daily for 3	RCT, MC Patients 12-75 years of age with clinically diagnosed	N=203 19-23 days	Primary: Clinical response and bacteriologic response	Primary: A satisfactory clinical response (judged as cured or improved) was observed in 94% of azithromycin patients and 95% of clarithromycin patients (P=0.518).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days vs clarithromycin 250 mg BID for 10 days	community-acquired pneumonia			In the azithromycin patients, 97% of pathogens were considered eradicated and 91% of pathogens were considered eradicated in the clarithromycin group.
Muller[73] (1993) Azithromycin 500 mg daily for 3 days vs clarithromycin 250 mg BID for 10 days	RCT, OL, MC Patients 12 years of age and older with acute upper respiratory infections	N=380 14 to 28 days	Primary: Clinical response and bacteriologic response	Primary: No significant difference was found between the 2 groups in clinical response for any diagnosis (P>0.05). Bacteriologic response was also similar between groups.
Aoyama et al.[55] (1996) Azithromycin 10 mg/kg daily for 5 days vs clarithromycin 10 mg/kg/day in 2 divided doses for 7 days vs erythromycin standard regimens	CS Patients with culture- positive pertussis Each patient was matched with 2 erythromycin-treated patients with culture-positive pertussis recruited from historical controls	N=17 2 weeks posttreatment	Primary: Eradication rates	Primary: Eradication rates 1 week after treatment were 100% in the clarithromycin and 89% in the matched erythromycin group, and 100% in the azithromycin group and 81% in the matched erythromycin group. Eradication rates 2 weeks after treatment were 100% in all groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
40-50 mg/kg/day for 2 weeks				
Altunaiji et al.[86] (2007) Azithromycin vs clarithromycin vs erythromycin	MA Patients with pertussis	N=2197 (13 trials) Variable duration	Primary: Clinical response rates	Primary: Short-term antibiotics (azithromycin for 3 to 5 days, clarithromycin for 7 days, or erythromycin for 7 days) were as effective as long-term antibiotics (erythromycin for 10 to 14 days) in eradicating *Bordetella pertussis* from the nasopharynx (RR, 1.02; 95% CI, 0.98 to 1.05), but were associated with fewer adverse events (RR, 0.66; 95% CI, 0.52 to 0.83). Trimethoprim/sulfamethoxazole for 7 days was also effective. There were no differences in clinical outcomes or microbiological relapse between short and long-term antibiotics. Contact prophylaxis of contacts older than six months of age with antibiotics did not significantly improve clinical symptoms or the number of cases developing culture-positive *B. pertussis*.
Castaldo et al.[39] (2003) Azithromycin 500 mg on day 1, then 250 mg daily for days 2-5 vs dirithromycin 500 mg daily for 5 days	RCT, SB, PG, MC Patients 35 years of age and older who are smokers or ex-smokers with an acute exacerbation of chronic bronchitis	N=86 35 days	Primary: Clinical success rates at the early (7-10 days) and the late (25-35 days) posttreatment visits	Primary: Clinical efficacy was observed in 84.8% of patients in the dirithromycin group and 75.7% in the azithromycin group at the early post-treatment visit. No significant difference was observed. Clinical efficacy was observed in 95.5% of patients in the dirithromycin group and 86.5% in the azithromycin group at the late post-treatment visit. No significant difference was observed.
Schonwald et al.[61] (1990) Azithromycin 250 mg BID on day 1 and 250 mg daily on days 2-5	RCT, MC, OL Patients 12 years of age and older with a diagnosis of atypical pneumonia	N=101 21 days posttreatment	Primary: Clinical response to treatment	Primary: There was no significant difference between the azithromycin group and erythromycin group in clinical response to treatment. Very good efficacy was reported in 82% of azithromycin patients and 84% of erythromycin patients. Good efficacy was reported in 18% of azithromycin patients and 16% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs erythromycin 500 mg QID for 10 days				erythromycin patients. No clinical failures were reported in either group.
Murray et al.[35] (2005) Azithromycin 2 g as a single dose vs levofloxacin 500 mg daily for 10 days	RCT, MC, DB, DD Patients 18 years of age and older with acute bacterial sinusitis	N=541 24 days	Primary: Clinical response at test-of-cure (TOC) day Secondary: Bacteriologic response and clinical response by baseline pathogen	Primary: The clinical cure at the TOC visit was 94.5% in the azithromycin group compared to 92.8% in the levofloxacin group. No significant differences were found between groups. Secondary: Bacteriologic response and clinical response by baseline pathogen were not statistically significant between groups.
Griffin et al.[105] (2010) Azithromycin or clarithromycin vs levofloxacin	RETRO Patients with *Legionella* pneumonia	N=39 Variable duration	Primary: Time to clinical stability (TCS) and length of hospital stay (LOS)	Primary: The mean TCS for the macrolide group was 5.1 days and 4.3 days for the levofloxacin group (P=0.43). The mean LOS for the macrolide group was 12.7 days and 8.9 days for the levofloxacin group (P=0.10).
Ioannidis et al.[72] (2001) Azithromycin at various doses given for 3-5 days vs amoxicillin-clavulanate, cefaclor,	MA Patients with acute otitis media, sinusitis, or pharyngitis	N=7,610 10 days	Primary: Clinical failure rate	Primary: Azithromycin had similar clinical failure rates compared to the comparator antibiotics. The difference in clinical failure rates was <0.5% and no significant difference was found between groups. No significant difference was observed in bacteriologic outcomes.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clarithromycin, roxithromycin, amoxicillin, erythromycin, penicillin				
Tamm et al.[88] (2007) Azithromycin 500 mg IV once daily for 2–5 days plus ceftriaxone 1 to 2 g IV once daily, followed by step-down to oral azithromycin 500 mg once daily for a total therapy duration of 7–10 days vs ceftriaxone 1 to 2 g IV once daily plus either clarithromycin 500 mg IV BID or erythromycin 1 g IV TID for 2 to 5 days, followed by step-down to either oral clarithromycin 500 mg BID or erythromycin 1 g	RCT, MC, OL Patients with moderate-to-severe community-acquired pneumonia (CAP) requiring hospitalization	N=135 28-35 days	Primary: Clinical and bacteriological response rates Secondary: Health care resource utilization	Primary: In the clinically evaluable population, the clinical response to ceftriaxone plus azithromycin and ceftriaxone plus clarithromycin/erythromycin was similar at both the end-of-study (EOS) and end-of-therapy (EOT) evaluations. Clinical success rates at EOT were 84.3% for ceftriaxone plus azithromycin and 82.7% for ceftriaxone plus clarithromycin/erythromycin (P=NS). Success rates at EOS were 81.7% for ceftriaxone plus azithromycin, and 75.0% for ceftriaxone plus clarithromycin/erythromycin. In the clinically evaluable population, success rates were 83% and 87%, respectively, at EOT, and 79% and 78%, respectively, at EOS (P=NS). Bacteriological eradication rates at EOT and EOS were similar for the two treatment groups in the bacteriological evaluable population. In the bacteriological MITT population, bacteriological eradication rates were greater at both EOT and EOS for the ceftriaxone plus azithromycin group (73.2% and 68.3%, respectively) compared with the ceftriaxone plus clarithromycin/erythromycin group (67.4% and 60.9%, respectively; P=NS). Secondary: In the group treated with ceftriaxone plus azithromycin, the mean hospital LOS was 10.7 days compared with 12.6 days for patients treated with ceftriaxone plus clarithromycin/erythromycin (P=NS). The total duration of intravenous and oral therapy was 9.5 days compared with 10.5 days for patients treated with ceftriaxone plus azithromycin as compared to ceftriaxone plus clarithromycin/erythromycin (P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
TID for a total of 7–14 days				The mean time from intravenous initiation to oral switch was 5.0 days for patients treated with ceftriaxone plus azithromycin, and 4.7 days for patients treated with ceftriaxone plus clarithromycin/erythromycin (P=NS). The incidence of infusion-related adverse events was 16.3% and 25.2%, respectively (P<0.04).
Rechtweg et al.[36] (2004) Clarithromycin 500 mg BID for 14 days vs amoxicillin-clavulanate 500 mg TID for 14 days (A-C)	RCT, SB Patients with uncomplicated acute rhinosinusitis	N=22 4 weeks	Primary: Results of 5 surveys completed by the patients	Primary: The Allergy Outcomes Survey (AOS) failed to demonstrate a significant improvement from baseline in any patient in either group (P>0.48). At day 28, the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) showed significant improvement in symptoms from baseline in both groups (P=0.003). The Short Form-36 (SF-36) failed to demonstrate a significant change in patients' global perception of their health at either day 14 or day 28 for all patients in both groups (P>0.25). The Symptom Severity Survey (SSS-6) indicated that there was a significant improvement in the clarithromycin patients at day 14 (P=0.02) and day 28 (P=0.03). The A-C patients demonstrated a significant improvement at day 28 (P=0.05), but not at day 14 (P=0.54). The Visual Analogue Scale (VAS) failed to demonstrate a significant improvement in symptoms at day 14 and day 28 in either group (P>0.30).
Gotfried et al.[40] (2005) Clarithromycin 500 mg BID for 7 days vs clarithromycin	RCT, DB, MC Patients 40 years of age and older with a presumptive diagnosis of an acute exacerbation of chronic bronchitis	N=485 40 days	Primary: Clinical cure, bacteriologic cure, target pathogen eradication rates at test-of-cure (TOC) visit (days 14-40)	Primary: Clinical cure rates were similar between groups (84% for both groups). Bacteriologic cure rates were 89% in the regular release group and 87% in the extended-release group. The overall pathogen eradication rates were 89% in the regular release group and 88% in the extended-release group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
extended-release 1,000 mg daily for 5 days				
Gotfried et al.[91] (2007) Clarithromycin extended-release (ER) 1,000mg once daily for 5 days vs clarithromycin immediate-release (IR) 500 mg twice daily for 7 days or telithromycin 800 mg once daily for 5 days	RCT, DB, MC Patients ≥35 years of age with a presumptive diagnosis of acute bacterial exacerbation of chronic bronchitis (ABECB)	N=818 8-40 days	Primary: Clinical bacteriological responses	Primary: The clinical cure rate in clinically evaluable patients at the follow-up visit was 90% each for the clarithromycin ER group and the comparator group (95% CI, -4.4 to 4.3). No significant between-group differences were observed in clinically evaluable patients based on resolution or resolution/improvement at the follow-up visit of the most common pretreatment signs/symptoms. The overall target pathogen eradication rate was 92% for the clarithromycin ER group and 93% for the comparator group at the follow-up visit (95% CI, –6.5 to 3.6). The bacteriological cure rate in clinically and bacteriologically evaluable patients was 92% for the clarithromycin ER group and 93% for the comparator group at the follow-up visit (95% CI, –7.3 to 3.9). The study drugs were well tolerated, with 1.9% of clarithromycin ER-treated patients and 1.5% of comparator-treated patients prematurely discontinuing treatment due to a drug-related adverse event(s). The overall incidence of drug-related adverse events was 18% in the clarithromycin ER group and 24% in the comparator group. The most common drug-related adverse events (>2% of patients) or those with a statistically significant difference in incidence between groups were: abdominal pain (0.2% and 1.7% in the clarithromycin ER and comparator groups, respectively; P=0.037), diarrhea (2.4% and 4.7%, respectively; P=NS), nausea (2.7% and 4.4%, respectively; P=NS), and abnormal taste (2.4% and 4.7%, respectively; P=NS). Clarithromycin ER-treated patients reported fewer episodes of abdominal pain than did patients treated with a comparator agent (0.2% vs 1.7%, respectively; P=0.037).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lee et al.[89] (2008) Clarithromycin 15 mg/kg/day twice daily vs erythromycin 30-50 mg/kg/day four times daily	RCT Children <15 years of age with community-acquired pneumonia	N=97 10 days	Primary: Clinical cure rate Secondary: Adverse events	Primary: All children with mycoplasma or chlamydia infections were cured clinically at the end of the study period. Delayed defervescence was observed in 18% of clarithromycin-treated children and in 20% of erythromycin-treated children (P>0.05). Gastrointestinal side effects, including vomiting, abdominal pain and diarrhea, were observed in 6% of children receiving clarithromycin and in 22% receiving erythromycin (P=0.039).
Garrido et al.[62] (2005) Inpatient: Clarithromycin IV or orally vs levofloxacin IV or orally Outpatient: Azithromycin orally vs clarithromycin orally vs levofloxacin orally	PRO, OS Patients with *Legionella* pneumonia	N=292 12 weeks	Primary: Clinical response	Primary: There was no significant difference in clinical response between groups in patients with mild to moderate pneumonia (P<0.08). Significantly more patients with severe disease treated with clarithromycin were more likely to have complications and longer hospital stays compared to those treated with levofloxacin (P<0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rifampicin was prescribed concomitantly to 45 patients treated with levofloxacin and 2 patients treated with clarithromycin.				
Ruiz-González et al.[94] (2007) Clarithromycin 500 mg BID, cefuroxime axetil 500 mg BID, or amoxicillin-clavulanate 875/125 TID for 10 days vs levofloxacin 500 mg once daily for 10 days	RCT, OL Patients >40 years old with an acute exacerbation of COPD	N=116 6 months	Primary: Mortality due to an exacerbation; number of exacerbations; need for hospitalization due to an exacerbation; infection-free interval time; pulse oximetry; lung function measured by spirometry	Primary: During follow up, 29 patients (31.2%) experienced no exacerbations while 45 (48.4%), 13 (14.0%), three (3.2%), two (2.2%) and one (1.1%) experienced one, two, three, four and five exacerbations, respectively. Overall, 19 (20.4%) patients died. At the end of the study, eight (18%) patients and 11(23%) patients assigned to levofloxacin and standard group, respectively, died due to an exacerbation (P=0.53). No differences were found in pulse oximetry, pulmonary function or quality of life at 1-month and 6-month follow up between groups. No differences were found in the number of exacerbations or infection-free interval between groups. However, 12 out of 33 (33.6%) AE-COPD treated with levofloxacin required in-hospital management in contrast to 27 out of 41 (65.8%) treated with the comparator (P=0.02).
Falagas et al.[92] (2008) Clarithromycin vs quinolones vs	MA Patients with an acute exacerbation of chronic bronchitis (AECB)	N=3,083 (7 trials) Variable duration	Primary: Treatment success, adverse events, mortality	Primary: There was no difference between the short- and long-duration therapies with regard to treatment success in intention-to-treat (RR 0.99, 95% CI, 0.95-1.03) clinically evaluable (RR 0.99, 95% CI, 0.96-1.02) or microbiologically evaluable (RR 0.98, 95% CI, 0.93-1.02) patients. Patients with AECB who received short- compared with long-duration antimicrobial therapy experienced fewer adverse events (RR 0.84, 95% CI, 0.72–0.97).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cefixime				No difference was found between the compared groups with regard to the number of patients withdrawn due to toxicity (RR 0.93, 95% CI 0.55–1.57) and the number of patients with drug-related diarrhea (RR 1.02, 95% CI 0.69–1.51). There was no difference regarding mortality between short- and long-duration antimicrobial regimens for the treatment of ITT patients with AECB (RR 0.73, 95% CI 0.16–3.27).
Hoppe et al.[56] (1989) Erythromycin ethylsuccinate 50-80 mg/kg/day in 3 doses for 14 days vs sulfamethoxazole-trimethoprim (SMX-TMP) 6-10 mg/kg/day of trimethoprim in 2 doses for 14 days	RCT, PRO Patients 9 months to 11 years of age with suspected early whooping cough	N=55 14 days	Primary: Clinical response to treatment	Primary: Clinical response to treatment was similar between groups with an improvement rate of 78.6% for erythromycin and 81.5% for SMX-TMP.
Esposito et al.[58] (1998) Erythromycin ethylsuccinate 15 mg/kg TID for 10 days vs cefaclor 25 mg/kg BID for 10 days	RCT Patients 2 to 12 years of age with acute pharyngotonsillitis	N=245 30 days	Primary: Clinical outcomes and bacteriologic outcomes	Primary: On day 10, clinical cure and microbiologic eradication was observed in 91.9% of patients in the cefaclor group, 90.5% in the amoxicillin-clavulanate group, and 76.8% in the erythromycin group. At day 30, bacteriologic recurrence was observed in 5 patients in the cefaclor group, 3 in the amoxicillin-clavulanate group, and 4 in the erythromycin group. The clinical and bacteriologic cure rates were significantly higher in the cefaclor and amoxicillin-clavulanate groups compared to the erythromycin group ($P<0.05$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amoxicillin-clavulanate 15 mg/kg TID for 10 days				
Macfarlane et al.[63] (1983) Erythromycin lactobionate 300 mg IV every 6 hours for 48 hours, followed by erythromycin stearate 500 mg orally QID for 7 days vs ampicillin 500 mg IV every 6 hours for 48 hours, followed by amoxicillin 500 mg orally QID for 7 days	RCT, DB Patients <80 years of age with primary pneumonia, including Legionnaires' disease	N=122 9 days	Primary: Clinical response to therapy (categorized as uncomplicated recovery, complicated recovery, or fatality)	Primary: Clinical response to therapy in all categories was similar between the groups.
Mandel et al.[82] (1991) Erythromycin-sulfisoxazole 50 mg/kg/day of erythromycin component and	RCT, DB Patients 7 months to 12 years of age with otitis media with effusion and without symptoms of acute otitis media	N=331 12 weeks	Primary: Proportion of patients effusion-free at 2 and 4 weeks in the erythromycin-sulfisoxazole and cefaclor groups	Primary: There were no significant differences in the proportion of patients who were effusion-free in the erythromycin-sulfisoxazole or cefaclor group compared to the amoxicillin group at week 2 or 4 (P>0.39). Secondary: There were no significant differences between groups in the recurrence rate of MEE after antibiotic therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
150 mg/kg/day of sulfisoxazole component in 4 divided doses vs amoxicillin 40 mg/kg/day in 3 divided doses vs cefaclor 40 mg/kg/day in 3 divided doses vs placebo	(otalgia, fever)		compared to the amoxicillin group Secondary: Recurrence rate of middle ear effusion (MEE) following antibiotic therapy, speech recognition threshold at 2 and 4 weeks	Speech recognition threshold was statistically higher in both the right and left ears in the placebo group than in the antimicrobial groups at 2 weeks (P<0.04). At 4 weeks, this difference was only present in the right ear (P=0.03), not in the left ear (P=0.19).
Rodriguez et al.[83] (1985) Erythromycin-sulfisoxazole vs amoxicillin	RCT, CS Patients with acute otitis media	N=145 28 days	Primary: Cure rates Secondary: Cure rates based on organism, occurrence of middle ear effusions	Primary: Cure rates at 10-14 days for infections due to all organisms was 83% in the amoxicillin group and 89% in the erythromycin-sulfisoxazole group. Secondary: Cure rates in patients infected with *H influenzae* were 84% in the amoxicillin group and 83% in the erythromycin-sulfisoxazole group. Cure rates in patients infected with *S pneumoniae* were 82% in the amoxicillin group and 98% in the erythromycin-sulfisoxazole group. Cure rates in patients infected with ampicillin-resistant *Haemophilus* were 100% in the amoxicillin group (1/1) and 88% in the erythromycin-sulfisoxazole group (7/8), and one patient had persistent otitis media at day 10. By day 10-14, 38% of patients in the amoxicillin group had a middle ear

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				effusion compared to 48% in the erythromycin-sulfisoxazole group. By day 28, 10% of patients in the amoxicillin group had a middle ear effusion compared to 16% in the erythromycin-sulfisoxazole group.
van Rensburg et al.[64] (2005) Telithromycin 800 mg daily for 7 days	OL Patients ≥13 years of age with community-acquired pneumonia	N=831 24 days	Primary: Clinical response, bacteriologic response	Primary: Clinical cure and bacteriologic eradication were seen in 15 of 16 patients infected with erythromycin-resistant *Streptococcus pneumonia* (ERSP) and/or penicillin- resistant *Streptococcus pneumonia* (PRSP). The overall clinical cure rate was 89.3% and bacteriologic eradication was observed in 87.6% of patients.
van Rensburg et al.[65] (2005) Telithromycin 800 mg daily for 5-10 days	MA Patients ≥18 years of age with community-acquired pneumonia	N=327 (9 trials) 24-28 days	Primary: Clinical response, bacteriologic response	Primary: The clinical cure rate with telithromycin was 91.2%. Thirty-five patients had infections caused by strains resistant to erythromycin and of these, clinical cure was established in 88.6%. Clinical failure was recorded in 4 patients with penicillin- and/or erythromycin-resistant pneumococci. Thirteen patients had penicillin- and/or erythromycin- resistant pneumococcal bacteremia. Clinical cure was established in 84.6% of resistant isolates compared to 90.2% of all pneumococcal bacteremia. The overall rate of satisfactory bacteriologic outcomes was 90.4%. In patients infected with isolates demonstrating reduced susceptibility to penicillin and/or erythromycin, eradication was achieved in 93.4%.
Fogarty et al.[43] (2005) Telithromycin 800 mg daily for 5 days vs clarithromycin	RCT (Pooled analysis) Patients ≥18 years of age with an acute exacerbation of chronic bronchitis	N=1,254 31 to 36 days	Primary: Clinical outcome at the test-of-cure (TOC) visit (days 17-24) and the late post-therapy visit (days 31-36), bacteriologic outcomes at the TOC visit and at	Primary: Pooled analysis of the clinical cure rates for all 3 studies indicates equivalence between the telithromycin groups and all comparators at the TOC visit. Clinical cure rates described above were reported as 86.0% for the telithromycin groups and 85.8% for the comparator groups at the TOC visit. Pooled analysis of the clinical cure rates for all 3 studies indicates

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
500 mg BID for 10 days vs amoxicillin-clavulanate 500 mg TID for 10 days vs cefuroxime 500 mg BID for 10 days			the late post-therapy visit	equivalence between the telithromycin groups and all comparators at the late post-therapy visit. Clinical cure rates described above were reported as 79.1% for the telithromycin groups and 78.7% for the comparator groups at the late post-therapy visit. A satisfactory bacteriologic outcome was achieved in 77.2% of patients in the telithromycin groups compared to 79.1% of patients in the comparator groups.
Aubier et al.[42] (2002) Telithromycin 800 mg daily for 5 days vs amoxicillin-clavulanate 500 mg TID for 10 days	RCT, DB, PG Patients ≥18 years of age with an acute exacerbation of chronic bronchitis	N=325 31 to 36 days	Primary: Clinical cure rate at the test-of-cure (TOC) visit (days 17-21) Secondary: Clinical cure rate at the late post-therapy visit (days 31-36), bacteriologic outcomes at the TOC visit (days 17-21) and late post-therapy visit (days 31-36)	Primary: There was no significant difference in clinical cure rates between groups at the TOC visit (86.1% for telithromycin and 82.1% for the amoxicillin-clavulanate group). Secondary: There was no significant difference in clinical cure rates at the late post-therapy visit between groups (78.1% for telithromycin and 75.0% for amoxicillin-clavulanate). Bacteriologic outcome was judged as satisfactory in 69.2% of patients in the telithromycin group and 70.0% of patients in the amoxicillin-clavulanate group.
Desrosiers et al.[90] (2008) Telithromycin 800 mg once daily for	OL, MC Patients ≥18 years old with clinical and radiological	N=298 Up to 49 days	Primary: Clinical success, adverse events, and quality of life	Primary: The per-protocol clinical success rate measured at the test-of-cure visit was 88.6% with telithromycin compared to 88.8% in the amoxicillin-clavulanate treatment group (95% CI, -8.9 to 8.5).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5 days vs amoxicillin-clavulanate 875 mg/125 mg twice daily for 10 days	diagnosis of acute bacterial sinusitis (ABS)			At the follow-up visit (days 41–49), 84.6% of patients in the telithromycin group achieved clinical success, compared with 84.8% of those in the amoxicillin–clavulanate group. Median times to reduction of total symptom scores were shorter for telithromycin vs amoxicillin–clavulanate (7 days vs 8 days [75% reduction] and 4 days vs 5 days [50% reduction] with the difference being statistically significant for the 50% reduction (P=0.044). Treatment-emergent adverse events (TEAEs) occurred in 20.7% of telithromycin-treated patients vs 31.8% of amoxicillin-clavulanate-treated patients (P=0.034). In the baseline SF-36 health questionnaire, 75.5% of patients (209/278) described themselves as feeling much or somewhat worse than a week earlier (telithromycin, 74.2% and amoxicillin–clavulanate, 76.6%).
Zervos et al.[41] (2003) Telithromycin 800 mg daily for 5 days followed by placebo for 5 days vs cefuroxime axetil 500 mg BID for 10 days	RCT, DB, PG Patients 18 years of age and older with a history of chronic bronchitis and diagnosed with an acute exacerbation	N=376 31-45 days	Primary: Clinical outcome at the test-of-cure (TOC) visit (days 17-24) Secondary: Clinical outcome at the late post-therapy visit, bacteriologic outcome at the TOC and late-post-therapy visits	Primary: There was no significant difference in clinical cure rates between the two treatment groups at the TOC visit. Secondary: There was no significant difference in clinical cure rates between the two groups at the late post-therapy visit. Bacteriologic outcomes were similar between the two groups at both the TOC and the late post-therapy visits.
Ferguson et al.[37] (2004) Telithromycin 800 mg daily for 5 days	RCT, DB, MC Patients 18 years of age and older with community-acquired acute bacterial sinusitis	N=349 36 days	Primary: Clinical response, bacteriologic response	Primary: Clinical success occurred in 87.4% of patients in the telithromycin group at the test-of-cure (TOC) visit (days 17-24) and in 86.9% of patients in the moxifloxacin group (P=0.8930). Clinical success occurred in 78.3% of patients in the telithromycin group at the late post-therapy visit (days 31-36) and in 78.8% of patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs moxifloxacin 400 mg daily for 10 days				moxifloxacin group (P=0.9227). Bacteriologic success occurred in 94.1% of telithromycin patients at the TOC visit and 93.9% of the moxifloxacin patients (P=0.9734).
Carbon et al.[66] (2006) Telithromycin 800 mg daily for 5-10 days vs amoxicillin, clarithromycin, trovafloxacin	MA Patients ≥18 years of age with community-acquired pneumonia	N=2,991 Up to 45 days	Primary: Clinical response, bacteriologic response	Primary: In patients with pneumococcal bacteremia treated with telithromycin, clinical cure was achieved in 90.2% in the per protocol population (PPb) and 80.9% in the bacteremic bacteriologic modified intent to treat (bmITT) population. Clinical cure was established in 78.9% of the PPb in the pooled analysis of all comparator antibiotics and in 62.5% of the bmITT population. Bacteriologic eradication was established in 93.9% of the PPb treated with telithromycin and 84.0% of patients in the bmITT population. Bacteriologic eradication was established in 78.9% of the PPb population in the pooled analysis of all comparator antibiotics and in 66.7% of the bmITT population. The study was not able to detect statistical differences between telithromycin and comparator antibiotics due to the small number of patients treated with comparators.
Miscellaneous Infections				
Dunne et al.[50] (2000) Azithromycin 250 mg daily vs azithromycin 600 mg daily vs	RCT, DB, DD, MC Patients ≥13 years of age with a positive blood culture for MAC within the previous 2 months, infected with the human immunodeficiency virus (HIV) and expected to survive	N=239 24 weeks of treatment with follow-up every 3 months	Primary: Sterilization (2 consecutive negative blood cultures for MAC at week 24) Secondary: Time to sterilization, change from baseline in level of	Primary: No significant differences were found between the azithromycin 600 mg group and the clarithromycin group in the primary endpoint. Secondary: No significant differences were found between the azithromycin 600 mg group and the clarithromycin group in any secondary endpoint. This study did not enroll the target of 200 participants; therefore, the power of the study to conclude equivalence between the 2 arms was only 61%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clarithromycin 500 mg BID	for at least 2 months, and who had not received therapy for MAC since the positive blood culture		mycobacteremia, durability of sterilization, mortality, clinical response judged by the investigator, change in quality of life, and patient tolerance for each regimen	
Peirce et al.[51] (1996) Clarithromycin 500 mg BID vs placebo	RCT, PC, DB, MC Patients >12 years of age with HIV infection	N=682 10 months	Primary: Time from randomization to the detection of disseminated infection with *M avium* complex (MAC) as evidenced by a positive blood culture or positive culture at another usually sterile site Secondary: Effect of clarithromycin on survival	Primary: *M avium* complex infection developed in 19 of the 333 patients (6%) in the clarithromycin group and in 53 of the 334 patients (16%) in the placebo group (P<0.001). Secondary: During the follow-up period of 10 months, 32% of patients in the clarithromycin group died and 41% in the placebo group died (P=0.026).
Benson et al.[52] (2000) Clarithromycin 500 mg BID vs rifabutin 450 mg	RCT, MC, DB, PC Patients 12 years of age and older with HIV infection and no signs or symptoms of *Mycobacterium avium* complex	N=1,216 ~595 days	Primary: Development of MAC disease as evidenced by a positive blood culture or positive culture at another usually sterile site	Primary: Of those patients who developed MAC disease, 9% were in the clarithromycin group, 15% were in the rifabutin group, and 7% were in the combination group. Patients who received rifabutin were more likely to develop MAC compared to patients in the clarithromycin group (P=0.005) or the combination group (P=0.0003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
once daily vs combination therapy at the same doses	(MAC) disease		Secondary: Death, treatment-limiting adverse effects	There was no significant difference in the time to development of MAC disease for clarithromycin compared to combination therapy (P=0.36). Secondary: There were no differences between groups in survival rates (P>0.28). Patients in the combination therapy group were more likely to discontinue treatment compared to patients in the clarithromycin group and the rifabutin group (P<0.0001). There was no significant difference between the rifabutin and clarithromycin group (P=0.29).
Stenberg et al.[46] (1991) Erythromycin ethylsuccinate 200 mg divided into 2 doses for 10 days (neonates) or erythromycin stearate 1,000 mg divided into 2 doses for 10 days (adults) vs roxithromycin 50 mg divided into 2 doses for 10 days (neonates) or 300 mg divided into 2 doses for 10 days (adults)	RCT, SB Neonates and adults with chlamydial conjunctivitis	N=55 1 month posttreatment	Primary: Clinical response, bacteriologic response	Primary: All patients in the neonate and adult groups were cured except for one in the neonatal group and 3 in the adult group. There was no significant difference in the clinical cure rate between erythromycin and roxithromycin. Ten patients in the erythromycin group were still culture-positive at the follow-up compared with 6 patients in the roxithromycin group.
Kneen et al.[47] (1998) Erythromycin	RCT, OL Children <16 years of age clinically	N=86 4 weeks posttreatment	Primary: Time to fever clearance, membrane	Primary: The mean time to fever clearance was significantly shorter in the penicillin group compared to the erythromycin group (P=0.0004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ethylsuccinate 50 mg/kg/day for 10 days vs benzylpenicillin 50,000 units/kg/day IM for 5 days followed by oral penicillin V 50 mg/kg/day for 5 days	diagnosed with diphtheria		clearance, and bacteriologic clearance	The median time to membrane clearance was the same in both treatment groups. The median time to bacteriologic clearance was the same in both treatment groups.

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily, IM=intramuscular, IV=intravenous
Study abbreviations: CS=comparative study, DB=double blind, DD=double dummy, ITT=intent-to-treat, MA=meta-analysis, MC=multi-center, OL=open label, OS=observational study, PC=placebo controlled, PG=parallel group, PP=per protocol, PRO=prospective trial, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind, SC=single center

Additional Evidence

Dose Simplification:
Several studies have assessed the effects of dosing regimens on compliance with antibiotics. Adair et al. compared azithromycin as a single dose to erythromycin administered every 6 hours in the treatment of *Chlamydia* infections in pregnant females.[79] Significantly more patients were compliant with the azithromycin regimen compared to the erythromycin regimen; however, efficacy was similar among the treatment groups. Significantly fewer gastrointestinal side effects were noted in the azithromycin group compared to the erythromycin group.

Lebel et al. compared clarithromycin administered twice daily to erythromycin administered 3 times daily in children with pertussis.[95] Efficacy was similar among the treatment groups; however, patients in the clarithromycin group experienced significantly fewer adverse events compared to patients in the erythromycin group (45% and 62%, respectively, P=0.035). Compliance was significantly higher in the clarithromycin group compared to the erythromycin group (98.5% vs 88.6%, respectively; P<0.001).

Stable Therapy:
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits:
Milstone et al. analyzed outcomes in patients with an acute exacerbation of chronic bronchitis receiving treatment with azithromycin for 3 days or usual care for 5 to 14 days.[80] The usual care group included quinolones, amoxicillin-clavulanate, clarithromycin, or β-lactams. Patients completed two quality-of-life questionnaires. Both groups recorded similar improvements in signs and symptoms of infection, absenteeism, use of concomitant respiratory medications, health care resource utilization, compliance, and treatment satisfaction.

Burgess et al. analyzed outcomes in patients with pneumonia who were initially treated with erythromycin, clarithromycin, azithromycin, and/or a non-pseudomonal third generation cephalosporin.[81] Results indicate no significant difference in patients who did or did not receive a macrolide in terms of comorbid illness, length of hospital stay, length of intravenous antibiotic therapy or mortality.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 11. Relative Cost of the Macrolides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Azithromycin	extended-release suspension, injection, suspension, tablet	Zithromax®*, Zithromax Tri-Pak®*, Zmax®	$$-$$$	$-$$
Clarithromycin	extended-release tablet, suspension, tablet	Biaxin®*, Biaxin XL®*	$$$-$$$$	$-$$$
Erythromycin base	delayed-release capsule, coated-particle tablet, delayed-release tablet, tablet	PCE®	$$$	$
Erythromycin ethylsuccinate	suspension, tablet	E.E.S. 200®, E.E.S. 400®*, EryPed 200®, EryPed 400®	$-$$$	$
Erythromycin ethylsuccinate and sulfisoxazole	suspension	N/A	N/A	$
Erythromycin lactobionate	injection	Erythrocin Lactobionate®	$$$-$$$$$	N/A
Erythromycin stearate	tablet	Erythrocin Stearate®	$-$$	N/A
Fidaxomicin	tablet	Dificid®	$$$$$	N/A
Telithromycin	tablet	Ketek®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=not available

X. Conclusions

The macrolides are approved to treat a variety of infections, including dermatologic, gastrointestinal, genitourinary, respiratory, as well as a variety of miscellaneous infections.[1-13] Several of the macrolides are available in a generic formulation, with the exception of erythromycin lactobionate, erythromycin stearate, fidaxomicin and telithromycin.

There are many guidelines that define the appropriate place in therapy for the macrolides. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the macrolide. The macrolides are recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, encephalitis, skin and soft-tissue infections, infectious diarrhea, *Helicobacter pylori* infections, sexually transmitted diseases, pertussis, community-acquired pneumonia, as well as prophylaxis and treatment of disseminated *Mycobacterium avium* disease in patients with HIV infection.[16-17,25-28,30-33,111,113-114,116-118] They are recommended as an alternative treatment option for otitis media, pharyngitis, sinusitis, infectious exacerbations of COPD, as well as for the prophylaxis of rheumatic fever.[18-22,29] Clinical trials have demonstrated comparable efficacy among the macrolides for the treatment of genital ulcers, upper/lower respiratory tract infections, and disseminated *Mycobacterium avium* disease.[38,43-44,55,57-59,61-62,64,73,79,86,88-89,91,104] The macrolides have also been shown to be comparable in efficacy to antibacterial agents in other classes.[34-35,37,41-43,45,48,53,56,63,67-68,70-72,74-76,78,82-83,87,90,92,94,96-97,102-103,105]

Fidaxomicin is a newer macrolide that is approved to treat *Clostridium difficile*-associated diarrhea (CDAD).[12] It is minimally absorbed after oral administration and has little or no activity against organisms other than clostridia. Guidelines recommend oral metronidazole or oral vancomycin for the treatment of CDAD.[107-108] Metronidazole is recommended for patients with mild to moderate disease, while vancomycin is recommended for patients with severe disease. First recurrences are generally treated like the initial episode; however, only vancomycin is used to treat the second or later recurrence of CDAD. Metronidazole should not be used beyond the first recurrence of CDAD, or for long-term chronic therapy, due to the potential for neurotoxicity.[109] Fidaxomicin was approved by the FDA in May 2011; therefore, there were no recommendations regarding this product in the guidelines. Louie et al. compared fidaxomicin and vancomycin in patients with CDAD (severity of disease not specified). Overall, clinical cure rates were similar among the treatment groups, and fidaxomicin was found to be non-inferior to vancomycin.[106] Recurrence was reported in 15.4% of patients treated with fidaxomicin compared to 25.3% of

patients treated with vancomycin (P=0.005). The lower rate of recurrence was seen in patients infected with the non-NAP1/BI/027 strains (7.8% with fidaxomicin vs. 25.5% with vancomycin; P<0.001). However, recurrence rates were similar among patients infected with the NAP1/BI/027 strain (24.4% with fidaxomicin vs. 23.6% with vancomycin; P=0.93).

Safety concerns with telithromycin have led to changes in the prescribing information, including stronger warnings regarding hepatotoxicity, visual disturbances and loss of consciousness.[13] There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis; therefore, telithromycin is contraindicated in this population. This agent is only indicated for the treatment of community-acquired pneumonia and there is a lack of data demonstrating clinical advantages over other macrolides.

Therefore, all brand macrolides within the class reviewed, with the exception of telithromycin, are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Telithromycin possesses an extensive adverse effect profile compared to the other brands, generics and OTC products in the class (if applicable) and should be managed through the existing medical justification portion of the prior authorization process.

XI. Recommendations

No brand macrolide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

No brand telithromycin product is recommended for preferred status, regardless of cost.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2010. Available from Wolters Kluwer Health, Inc. Accessed September 2011.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2010; September 2011.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed September 2011.
4. Zithromax® [package insert]. New York, NY: Pfizer, Inc.; January 2011.
5. Zmax® [package insert]. New York, NY: Pfizer, Inc.; June 2011.
6. Biaxin® [package insert]. North Chicago, IL: Abbott Laboratories: May 2011.
7. PCE® [package insert]. North Chicago, IL: Abbott Laboratories: April 2010.
8. E.E.S.® [package insert]. North Chicago, IL: Abbott Laboratories: June 2009.
9. EryPed® [package insert]. North Chicago, IL: Abbott Laboratories: November 2008.
10. Erythrocin Lactobionate® [package insert]. Lake Forest, IL: Hospira, Inc. June 2011.
11. Erythrocin Stearate® [package insert]. North Chicago, IL: Abbott Laboratories: June 2009.
12. Dificid® [package insert]. San Diego, CA: Optimer Pharmaceuticals, Inc.; May 2011.
13. Ketek® [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; December 2010.
14. Graziani AL**.** Azithromycin, clarithromycin, and telithromycin. In: UpToDate, Hooper, DC (Ed), UpToDate, Waltham, MA, 2011.
15. Mandell GL, Bennett JE, Dolin R. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 6th ed. Philadelphia, PA, Elsevier ; 2005.
16. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005 Nov 15;41(10):1373-406.
17. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1-110.
18. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatrics. 2004 May;113(5):1451-65.
19. Bisno A, Gerber M, Gwaltney J, Kaplan E, Schwartz R. Practice guideline for the diagnosis and management of group A Streptococcal pharyngitis. Clin Infect Dis 2002;35(2):113-25.
20. Slavin R ed, Spector S ed, Bernstein I ed. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol. 2005;116(6):S13-S47.
21. American Academy of Pediatrics subcommittee on the management of sinusitis and committee on quality improvement. Clinical practice guideline: management of sinusitis. Pediatrics. 2001;108(3):798-808.
22. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2010. 117 p. Available at: www.goldcopd.com. Accessed October 2011.
23. Braman SS. Chronic cough due to acute bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129 (1 Suppl): 95S-103S.
24. Braman SS. Chronic cough due to chronic bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129 (1 Suppl): 104S-15S.
25. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-72.
26. Ramsdell J, Narsavage GL, Fink JB; American College of Chest Physicians' Home Care Network Working Group. Management of community-acquired pneumonia in the home: an American College of Chest Physicians clinical position statement. Chest. 2005 May;127(5):1752-63.
27. Tiwari T, Murphy TV, Moran J; National Immunization Program, CDC. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines. MMWR Recomm Rep 2005;54(RR-14):1-16.
28. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009;58(RR-4):1-207.

29. Bonow R, Carabello B, Chatterjee K et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e1-142.
30. Chey W, Wong B. American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection. Am J Gastroenterol 2007; 102:1808-1825.
31. Hunt R, Fallone C, Veldhuyzan van Zanten S, Sherman P, et al., CHSG 2004 participants. Canadian Helicobacter Study Group Consensus Conference: Update on the management of *Helicobacter pylori*--an evidence-based evaluation of six topics relevant to clinical outcomes in patients evaluated for *H pylori* infection. Can J Gastroenterol. 2004; 18(9):547-554.
32. Malfertheiner P, Megraud F, O'Morain C., et al. Current Concepts in the Management of *Helicobacter pylori* Infection. The Maastricht 2-2000 Consensus Report. European *Helicobacter Pylori* Study Group. Aliment Pharmacol Ther 2002; 16:167-180.
33. Veldhuyzen van Zanten SJ, Flook N, Chiba N, Armstrong D, An evidence-based approach to the management of uninvestigated dyspepsia in the era of *Helicobacter pylori*. Canadian Dyspepsia Working Group. CMAJ. 2000; 162(suppl 12):S3-23.
34. Klapan I. Culig J, Orskovic K, Matrapazovski M, Radosevic S. Azithromycin versus amoxicillin-clavulanate in the treatment of acute sinusitis. Am J Otolaryngol. 1999;20(1):7-11.
35. Murray J, Emparanza P, Lesinskas E, Tawdrous M, Breen J. Efficacy and safety of a novel, single-dose azithromycin micropshere formulation versus 10 days of levofloxacin for the treatment of acute bacterial sinusitis in adults. Otolaryngol Head Neck Surg. 2005;133:194-201.
36. Rechtweg J, Moinuddin R, Houser S, Mamikoglu B, Corey J. Quality of life in treatment of acute rhinosinusitis with clarithromycin and amoxicillin-clavulanate. Laryngoscope. 2004;114:806-10.
37. Ferguson B, Guzzetta R, Spector S, Hadley J. Efficacy and safety of oral telithromycin once daily for 5 days versus moxifloxacin once daily for 10 days in the treatment of acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg. 2004;131(3):207-14.
38. Swanson R, Lainez-Ventosilla A, De Salvo M, Dunne M, Amsden GW. Once-daily azithromycin for 3 days compared with clarithromycin for 10 days for acute exacerbation of chronic bronchitis: a multicenter, double-blind, randomized study. Treat Respir Med. 2005;4(1):31-9.
39. Castaldo R, Celli B, Gomez F et al. A comparison of 5-day courses of dirithromycin and azithromycin in the treatment of acute exacerbations of chronic obstructive pulmonary disease. Clin Ther. 2003;25(2):542-57.
40. Gotfried M, Notario G, Spiller J, Palmer R, Busman T. Comparative efficacy of once daily, 5-day short-course therapy with clarithromycin extended release versus twice daily, 7-day therapy with clarithromycin immediate release in acute bacterial exacerbation of chronic bronchitis. Curr Med Res Opin 2005;21:245-54.
41. Zervos M, Heyder A, Leroy B. Oral telithromycin 800 mg once daily for 5 days versus cefuroxime axetil 500 mg twice daily for 10 days in adults with acute exacerbations of chronic bronchitis. J Int Med Res. 2003;31:157-69.
42. Aubier M, Aldons P, Leak A et al. Telithromycin is as effective as amoxicillin-clavulanate in acute exacerbations of chronic bronchitis. Respir Med. 2002;96:862-71.
43. Fogarty C, Zervos M, Tellier G et al. Telithromycin for the treatment of acute exacerbations of chronic bronchitis. Int J Clin Pract. 2005;59(3):296-305.
44. Tyndall M, Agoki E, Plummer F et al. Single dose azithromycin for the treatment of chancroid: a randomized comparison with erythromycin. Sex Transm Dis. 1994;21(4):231-4.
45. Martin D, Sargent S, Wendel G et al. Comparison of azithromycin and ceftriaxone for the treatment of chancroid. Clin Infect Dis. 1995;21:409-14.
46. Stenberg K, Mardh P. Treatment of chlamydial conjunctivitis in newborns and adults with erythromycin and roxithromycin. J Antimicrob Chemother. 1991;28:301-7.
47. Kneen R, Giao P, Solomon T et al. Penicillin vs erythromycin in the treatment of diphtheria. Clin Infect Dis. 1998;27:845-50.
48. Mantzaris G, Petraki K, Archavlis E et al. Omeprazole triple therapy versus omeprazole quadruple therapy for healing duodenal ulcer and eradication of *Helicobacter pylori infection*: a 24-month follow-up study. Eur J Gastroenterol Hepatol. 2002;14:1237-43.
49. Ohlin B, Cederberg A, Kjellin T, et al. Dual versus triple therapy in eradication of *Helicobacter pylori*. Hepatogastroenterology. 2002;49:172-5.

50. Dunne M, Fessel J, Kumar P et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated *Mycobacterium avium* infection in patients with human immunodeficiency virus. Clin Infect Dis. 2000;31:1245-52.
51. Peirce M, Crampton S, Henry D et al. A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced acquired immunodeficiency syndrome. N Engl J Med. 1996;335(6):384-91.
52. Benson C. Williams P, Cohn D et al. Clarithromycin or rifabutin alone or in combination for primary prophylaxis of *Mycobacterium avium* complex disease in patients with AIDS: a randomized, double-blind, placebo-controlled trial. J Infect Dis. 2000;181:1289-97.
53. Bevan C, Ridgway G, Rothermel D. Efficacy and safety of azithromycin as monotherapy or combined with metronidazole compared with two standard multi-drug regimens for the treatment of acute pelvic inflammatory disease. J Int Med Res. 2003;31:45-54.
54. Pichichero M, Hoeger W, Casey J. Azithromycin for the treatment of pertussis. Pediatric Infectious Disease Journal. 2003;22(9):847-9.
55. Aoyama T, Sunakawa K, Iwata S, Takeuchi Y, Fujii R. Efficacy of short-term treatment of pertussis with clarithromycin and azithromycin. Journal of Pediatrics. 1996;129(5):761-4.
56. Hoppe J, Halm U, Hagedorn H, Kraminer-Hagedorn A. Comparison of erythromycin ethylsuccinate and co-trimoxazole for treatment of pertussis. Infection. 1989;17(4):227-31.
57. Venuta A, Laudizi L, Beverelli A et al. Azithromycin compared with clarithromycin for the treatment of Streptococcal pharyngitis in children. J Int Med Res. 1998;26;152-8.
58. Esposito S, De Ritis G, D'Errico G, Noviello S, Ianniello F. Clinical comparison of cefaclor twice daily versus amoxicillin-clavulanate or erythromycin three times daily in the treatment of patients with Streptococcal pharyngitis. Clin Ther. 1998;20(1):72-9.
59. Drehobl M, De Salvo M, Lewis D, Breen J. Single-dose azithromycin microspheres vs clarithromycin extended-release for the treatment of mild-to-moderate community-acquired pneumonia in adults. Chest. 2005;128(4):2230-8.
60. O'Doherty B, Muller O et al. Randomized, multicentre study of the efficacy and tolerance of azithromycin versus clarithromycin in the treatment of adults with mild to moderate community-acquired pneumonia. Eur J Clin Microbiol Infect Dis. 1998;17:828-33.
61. Schonwald S, Gunjaca M, Kolacny-Babic L, Car V, Gosev M. Comparison of azithromycin and erythromycin in the treatment of atypical pneumonias. J Antimicrob Chemother. 1990;25(Suppl A):123-6.
62. Garrido R, Parra F, Frances L, et al. Antimicrobial chemotherapy for Legionnaire's disease: levofloxacin versus macrolides. Clin Infect Dis. 2005;40:800-6.
63. Macfarlane J, Finch R, Ward M, et al. Erythromycin compared with a combination of ampicillin and amoxicillin as initial therapy for adults with pneumonia including Legionnaires' disease. J Infect 1983;7:111-7.
64. van Rensburg D, Fogarty C, De Salvo M, Rangaraju M, Nusrat R. Efficacy of oral telithromycin in community-acquired pneumonia caused by resistant *Streptococcus pneumoniae*. J Infect. 2005;51:201-5.
65. van Rensburg D, Fogarty C, Kohno S, Dunbar L, Rangaraju M, Nusrat R. Efficacy of telithromycin in community-acquired pneumonia caused by pneumococci with reduced susceptibility to penicillin and/or erythromycin. Chemotherapy. 2005;51:186-92.
66. Carbon C, van Rensburg D, Hagberg L et al. Clinical and bacteriologic efficacy of telithromycin in patients with bacteremic community-acquired pneumonia. Respiratory Medicine. 2006;100:577-85.
67. Montero L. A comparative study of the efficacy, safety, and tolerability of azithromycin and cefaclor in the treatment of children with acute skin and/or soft tissue infections. J Antimicrob Chemother. 1996;37:125-31.
68. Amaya-Tapia G, Aguirre-Avalos G, Andrade-Villanueva J et al. Once-daily azithromycin in the treatment of adult skin and skin-structure infections. J Antimicrob Chemother. 1993;31(Suppl E):129-35.
69. Wasilewski M, Wilson M, Sides G, Stotka J. Comparative efficacy of 5 days of dirithromycin and 7 days of erythromycin in skin and soft tissue infections. J Antimicrob Chemother. 2000;46:255-62.
70. Hook E, Martin D, Stephens J, Smith B, Smith K. A randomized, comparative pilot study of azithromycin versus benzathine penicillin G for treatment of early syphilis. Sex Transm Dis. 2002;29(8):486-90.
71. Riedner G, Rusizoka M, Todd J et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. N Engl J Med. 2005;353(12):1236-44.
72. Ioannidis J, Contopoulos-Ioannidis D, Chew P, Lau J. Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for upper respiratory tract infections. J Antimicrob Chemother. 2001;48:677-89.

73. Muller O. Comparison of azithromycin versus clarithromycin in the treatment of patients with upper respiratory tract infections. J Antimicrob Chemother. 1993;31(Suppl E):137-46.
74. Martin D, Mroczkowski T, Dalu Z et al. A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis. N Engl J Med. 1992;327(13):921-5.
75. Lauharanta J, Saarinen K, Mustonen M, Happonen H. Single-dose oral azithromycin versus seven-day doxycycline in the treatment of non-gonococcal urethritis in males. J Antimicrob Chemother 1993;31:177-83.
76. Lister P, Balechandran T, Ridgway G, Robinson A. Comparison of azithromycin and doxycycline in the treatment of non-gonococcal urethritis in men. J Antimicrob Chemother. 1993;31(Suppl E):185-92.
77. Mikamo H, Sato Y, Hayasaki Y, Tamaya T. Adequate macrolide treatment schedules for uterine cervicitis caused by *Chlamydia trachomatis*. Chemotherapy. 1999;45:396-8.
78. Moller B, Herrmann B, Ibsen H et al. Occurrence of Ureaplasma urealyticus and Mycoplasma hominis in non-gonococcal urethritis before and after treatment in a double-blind trial of ofloxacin versus erythromycin. Scand J Infect Dis Suppl. 1990;68:31-4.
79. Adair C, Gunter M, Stovall T et al. Chlamydia in pregnancy: a randomized trial of azithromycin and erythromycin. Obstet Gynecol. 1998;91(2):165-8.
80. Milstone A, Patsimas J, Farzan et al. Prospective observational study of patient-reported outcomes for azithromycin versus usual care in the treatment of bacterial acute exacerbation of chronic bronchitis. Clin Ther. 2005;27(6):926-39.
81. Burgess D, Lewis J. Effect of macrolides as part of initial empiric therapy on medical outcomes for hospitalized patients with community-acquired pneumonia. Clin Ther. 2000;22(7):872-8.
82. Mandel E, Rockette H, Paradise J, Bluestone C, Nozza R. Comparative efficacy of erythromycin-sulfisoxazole, cefaclor, amoxicillin or placebo for otitis media with effusion on children. Pediatr Infect Dis J. 1991;10:899-906.
83. Rodriguez W, Schwartz W, Sait R, et al. Erythromycin-sulfisoxazole vs amoxicillin in the treatment of acute otitis media in children. A double-blind, multiple-dose comparative study. Am J Dis Child 1985;139:766-70.
84. Bai Z, Yang K, Liu Y, et al. Azithromycin vs benzathine penicillin G for early syphilis: a meta-analysis of randomized clinical trials. Int J STD AIDS. 2008 Apr;19(4):217-21.
85. Panpanich R, Lerttrakarnnon P, Laopaiboon M. Azithromycin for acute lower respiratory tract infections. Cochrane Database Syst Rev 2008;(1):CD001954.
86. Altunaiji S, Kukuruzovic R, Curtis N, et al. Antibiotics for whooping cough (pertussis). Cochrane Database Syst Rev. 2007 Jul 18;(3):CD004404.
87. Savaris R, Teixeira L, Torres T, et al. Comparing ceftriaxone plus azithromycin or doxycycline for pelvic inflammatory disease: a randomized controlled trial. Obstet Gynecol 2007;110:53-60.
88. Tamm M, Todisco T, Feldman C, et al. Clinical and bacteriological outcomes in hospitalised patients with community-acquired pneumonia treated with azithromycin plus ceftriaxone, or ceftriaxone plus clarithromycin or erythromycin: a prospective, randomised, multicentre study. Clin Microbiol Infect 2007;13:162-71.
89. Lee P, Wu M, Huang L, et al. An open, randomized, comparative study of clarithromycin and erythromycin in the treatment of children with community-acquired pneumonia. J Microbiol Immunol Infect 2008;41:54-61.
90. Desrosiers M, Ferguson B, Klossek J, et al. Clinical efficacy and time to symptom resolution of 5-day telithromycin versus 10-day amoxicillin-clavulanate in the treatment of acute bacterial sinusitis. Curr Med Res Opin 2008;24:1691-702.
91. Gotfried M, Busman T, Norris S, et al. Role for 5-day, once-daily extended-release clarithromycin in acute bacterial exacerbation of chronic bronchitis. Curr Med Res Opin. 2007 Feb;23(2):459-66.
92. Falagas M, Avgeri S, Matthaiou D, et al. Short- versus long-duration antimicrobial treatment for exacerbations of chronic bronchitis: a meta-analysis. J Antimicrob Chemother 2008;62:442-50.
93. Uygun A, Kadayifci A, Safali M, et al. The efficacy of bismuth containing quadruple therapy as a first-line treatment option for *Helicobacter pylori*. J Dig Dis 2007;8:211-5.
94. Ruiz-González A, Giménez A, Gómez-Arbonés X, et al. Open-label, randomized comparison trial of long-term outcomes of levofloxacin versus standard antibiotic therapy in acute exacerbations of chronic obstructive pulmonary disease. Respirology 2007;12:117-21.
95. Lebel M, Mehra S. Efficacy and safety of clarithromycin versus erythromycin for the treatment of pertussis: a prospective, randomized, single blind trial. Pediatr Infect Dis. 2001;20:1149-54.

96. Henry D, Riffer E, Sokol W, Chaudry N, Swanson R. Randomized double-blind study comparing 3- and 6-day regimens of azithromycin with a 10-day amoxicillin-clavulanate regimen for treatment of acute bacterial sinusitis. Antimicrob Agents Chemother. 2003;47(9):2770-4.
97. Hook EW 3rd, Behets F, Van Damme K, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. J Infect Dis 2010;201:1729-35.
98. Mena LA, Mroczkowski TF, Nsuami M, et al. A randomized comparison of azithromycin and doxycycline for the treatment of Mycoplasma genitalium-positive urethritis in men. Clin Infect Dis 2009;48:1649-54.
99. Marple BF, Roberts CS, Frytak JR, et al. Azithromycin extended release vs amoxicillin/clavulanate: symptom resolution in acute sinusitis. Am J Otolaryngol 2010;31:1-8.
100. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011;365:689-98.
101. Vukelic D, Trkulja V, Salkovic-Petrisic M. Single oral dose of azithromycin versus 5 days of oral erythromycin or no antibiotic in treatment of campylobacter enterocolitis in children: a prospective randomized assessor-blind study. J Pediatr Gastroenterol Nutr 2010;50:404-10.
102. Morris PS, Gadil G, McCallum GB, et al. Single-dose azithromycin versus seven days of amoxycillin in the treatment of acute otitis media in Aboriginal children (AATAAC): a double blind, randomised controlled trial. Med J Aust 2010;192:24-9.
103. Arguedas A, Soley C, Kamicker BJ, et al. Single-dose extended-release azithromycin versus a 10-day regimen of amoxicillin/clavulanate for the treatment of children with acute otitis media. Int J Infect Dis 2011;15:e240-8.
104. Jorgensen DM. Single-dose extended-release oral azithromycin vs 3-day azithromycin for the treatment of group A beta-haemolytic streptococcal pharyngitis/tonsillitis in adults and adolescents: a double-blind, double-dummy study. Clin Microbiol Infect 2009;15:1103-10.
105. Griffin AT, Peyrani P, Wiemken T, et al. Macrolides versus quinolones in Legionella pneumonia: results from the Community-Acquired Pneumonia Organization international study. Int J Tuberc Lung Dis 2010;14:495-9.
106. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 2011;364:422-31.
107. Kaushik JS, Gupta P, Faridi MM et al. Single dose azithromycin versus ciprofloxacin for cholera in children: a randomized 24 hours controlled trial. Indian Pediatr 2010;47:309-15.
108. Molina-Infante J, Perez-Gallardo B, Fernandez-Bermejo M et al. Clinical trial: clarithromycin vs levofloxacin in first-line triple and sequential regimens for *Helicobacter pylori* eradication. Aliment Pharmacol Ther 2010;31:1077-84.
109. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol 2010;31:431-55.
110. Bauer MP, Kuijper EJ, van Dissel JT, European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for *Clostridium difficile* infection (CDI). Clin Microbiol Infect 2009;15:1067-79.
111. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Eur Heart J 2009;30:2369-413.
112. Rosenfeld R, Andes D, Bhattacharyya N, et al. American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF). Clinical practice guideline: adult sinusitis. Otolaryngol Head Neck Surg 2007;137(Suppl 3):S1-31.
113. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011;53:e25-76.
114. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM, Whitley RJ, Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303-27.
115. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis. 2004;38:1706–15.
116. Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, et al; Infectious Diseases Society of America. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis. 2001;32:331-51.

117. Hill DR, Ericsson CD, Pearson RD, Keystone JS, Freedman DO, Kozarsky PE, et al. The practice of travel medicine: Guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006; 43:1499-1539.
118. World Gastroenterology Organization (WGO). WGO practice guideline: acute diarrhea. Munich, Germany: World Gastroenterology Organization (WGO); 2008 Mar. 28 p. http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/01_acute_diarrhea.pdf. Accessed December 2011.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Penicillins
AHFS Class 081216
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I. Overview

The penicillins are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-12] They are classified into five groups based on their spectrum of activity, including natural penicillins, penicillinase-resistant penicillins, aminopenicillins, carboxypenicillins, and ureidopenicillins.[13] Penicillins inhibit the synthesis of the bacterial peptidoglycan cell wall by binding to specific penicillin-binding proteins located inside the bacterial cell wall.

The natural penicillins (penicillin G and penicillin V) are active against many gram-positive and gram-negative cocci, gram-positive rods, and most anaerobes.[14] However, they are readily hydrolyzed by the enzyme penicillinase and are ineffective against most strains of *Staphylococcus aureus*. Penicillinase-resistant penicillins (dicloxacillin, nafcillin and oxacillin) have a narrower spectrum of activity than the natural penicillins. They are primarily active against penicillinase-producing strains of gram-positive cocci, particularly *Staphylococcus* species. Aminopenicillins (amoxicillin and ampicillin) have an extended spectrum of activity compared to the natural penicillins and penicillinase-resistant penicillins.[14] They are active against gram-negative bacilli, but not against penicillinase-producing staphylococci. They are also inhibitors of β-lactamases of gram-negative bacilli. Ticarcillin (carboxypenicillin) and piperacillin (ureidopenicillin) are active against *Pseudomonas aeroginosa*.[13] Their spectrum of activity is similar to the aminopenicillins; however, they have additional activity against gram-negative aerobic rods. They are susceptible to inactivation by beta-lactamases.

Bacteria have developed several mechanisms to counter the effects of penicillins. The most significant is the production of β-lactamases, which are enzymes that hydrolytically disrupt the β-lactam ring of the penicillin, rendering the penicillin ineffective. Another mechanism of resistance includes alteration of the penicillin-binding proteins within the bacteria so that their affinity for penicillins is decreased. Due to increased bacterial resistance, penicillins are combined with β-lactamase inhibitors, such as clavulanate, sulbactam, and tazobactam.[14] The β-lactamase inhibitors have a high, irreversible binding affinity for the β-lactamase enzyme and prevent hydrolysis of the penicillin β-lactam ring. They also bind to the penicillin-binding proteins of the bacteria, increasing the effectiveness of penicillin. However, they possess minimal antimicrobial activity by themselves; therefore, they are not used as monotherapy.

The penicillins that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The majority of the penicillins are available in a generic formulation, with the exception of penicillin G benzathine (with or without penicillin G procaine) and ticarcillin/clavulanate. This class was last reviewed in August 2009.

Table 1. Penicillins Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amoxicillin	capsule, chewable tablet, extended-release tablet, suspension, tablet	Moxatag®	amoxicillin
Amoxicillin and clavulanate	chewable tablet, extended-release tablet, suspension, tablet	Augmentin®*, Augmentin XR®*	amoxicillin and clavulanate
Ampicillin	capsule, injection, suspension	N/A	ampicillin
Ampicillin and sulbactam	injection	Unasyn®*	ampicillin and sulbactam
Dicloxacillin	capsule	N/A	dicloxacillin
Nafcillin	injection	N/A	nafcillin
Oxacillin	injection	N/A	oxacillin

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Penicillin G benzathine	injection	Bicillin L-A®	none
Penicillin G benzathine and penicillin G procaine	injection	Bicillin C-R®	none
Penicillin G potassium	injection	Pfizerpen®*	penicillin G potassium
Penicillin G procaine	injection	N/A	penicillin G procaine
Penicillin G sodium	injection	N/A	penicillin G sodium
Penicillin V potassium	suspension, tablet	N/A	penicillin V potassium
Piperacillin and tazobactam	injection	Zosyn®*	piperacillin and tazobactam
Ticarcillin and clavulanate	injection	Timentin®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

The penicillins have been shown to be active against the strains of microorganisms indicated in Tables 2-3. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the penicillins that are noted in Tables 5-6. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Penicillins (Drugs A-O)[1-12]

Organism	Amoxicillin	Amoxicillin/Clavulanate	Ampicillin	Ampicillin/Sulbactam	Dicloxacillin	Nafcillin	Oxacillin
Gram-Positive Aerobes							
Enterococcus faecalis	✔ †						
Enterococcus species			✔				
Listeria monocytogenes			✔				
Staphylococcus aureus		✔ †§	✔	✔			
Staphylococcus species	✔ †		✔		✔	✔	✔
Streptococcus pneumoniae	✔ †	✔ §	✔				
Streptococcus pyogenes	✔ §						
Streptococcus species	✔ †		✔				
Gram-Negative Aerobes							
Acinetobacter calcoaceticus				✔			
Enterobacter species		✔ †		✔			
Escherichia coli	✔ †	✔ †	✔	✔			
Haemophilus influenzae	✔ †	✔ †§	✔				
Haemophilus parainfluenza		✔ §					
Helicobacter pylori	✔ †						
Klebsiella pneumoniae		✔ §		✔			
Klebsiella species		✔ †		✔			
Moraxella catarrhalis		✔ †§					
Neisseria gonorrhoeae	✔ †		✔				
Neisseria meningitidis			✔				
Proteus mirabilis	✔ †		✔	✔			
Salmonella species			✔				
Salmonella typhosa			✔				
Shigella species			✔				
Anaerobes							
Bacteroides fragilis				✔			
Bacteroides species				✔			

†Immediate-release formulation
§Extended-release formulation

Table 3. Microorganisms Susceptible to the Penicillins (Drugs P-T)[1-12]

Organism	Penicillin G	Penicillin V	Piperacillin/Tazobactam	Ticarcillin/Clavulanate
Gram-Positive Aerobes				
Bacillus anthracis	✔ §			
Corynebacterium diphtheriae	✔ §			

Organism	Penicillin G	Penicillin V	Piperacillin/Tazobactam	Ticarcillin/Clavulanate
Erysipelothrix insidiosa	✔ §			
Listeria monocytogenes	✔ §			
Staphylococcus aureus			✔	✔
Staphylococcus epidermidis				✔
Staphylococcus species	✔ §	✔		
Streptococcus species	✔ †§	✔		
Gram-Negative Aerobes				
Acinetobacter baumanii			✔	
Alcaligenes faecalis	✔ §			
Citrobacter species				✔
Enterobacter cloacae				✔
Enterobacter species	✔ §			✔
Escherichia coli	✔ §		✔	✔
Haemophilus influenzae			✔	✔
Klebsiella pneumoniae			✔	✔
Klebsiella species				✔
Neisseria gonorrhoeae	✔ §			
Pasteurella multocida	✔ §			
Proteus mirabilis	✔ §			
Pseudomonas aeruginosa			✔	✔
Pseudomonas species				✔
Salmonella species	✔ §			
Serratia marcescens				✔
Shigella species	✔ §			
Spirillum minus	✔ §			
Streptobacillus moniliformis	✔ §			
Anaerobes				
Actinomyces species	✔ §			
Bacteroides fragilis			✔	✔
Clostridium species	✔ §			
Fusobacterium species	✔ §	✔		
Prevotella melaninogenicus				✔
Treponema pallidum	✔ §			

†Intramuscular formulation
§Intravenous formulation

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the penicillins are summarized in Table 4.

Table 4. Treatment Guidelines Using the Penicillins

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Guidelines on the Prevention, Diagnosis, and Treatment of Infective Endocarditis[116] (2009)**	• Antibiotic treatment of infective endocarditis due to oral streptococci and group D streptococci: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin or ceftriaxone for 4 weeks ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for 2 weeks ▪ Vancomycin for 4 weeks (in beta-lactam allergic patients) o Penicillin-resistant strains: ▪ Penicillin G or amoxicillin for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks plus gentamicin for 2 weeks (in beta-lactam allergic patients) • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for 4 to 6 weeks plus gentamicin for 3 to 5 days ▪ Vancomycin for 4 to 6 weeks plus gentamicin for 3 to 5 days (penicillin-allergic patients or methicillin-resistant staphylococci) o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks ▪ Vancomycin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks (penicillin-allergic patients or methicillin-resistant staphylococci) • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains ▪ Amoxicillin plus gentamicin for 4 to 6 weeks ▪ Ampicillin plus gentamicin for 4 to 6 weeks ▪ Vancomycin plus gentamicin for 6 weeks • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months ▪ Doxycycline plus quinolone for >18 months o *Bartonella* species: ▪ Ceftriaxone or ampicillin IV ▪ Doxycycline orally for 6 weeks plus gentamicin or netilmicin for 3 weeks o *Legionella* species: ▪ Erythromycin IV for 2 weeks, then orally for 4 weeks plus rifampin or ciprofloxacin orally for 6 weeks

Clinical Guideline	Recommendation(s)
	o *Mycoplasma* species: ▪ Newer fluoroquinolones for >6 months o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Penicillin G or streptomycin IV for 2 weeks, then cotrimoxazole orally for 1 year ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis (before or without pathogen identification): o Native valves: ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks o Prosthetic valves (early, <12 months post surgery) ▪ Vancomycin IV for 6 weeks, gentamicin IV for 2 weeks, and rifampin orally for 2 weeks o Prosthetic valves (late, ≥12 months post surgery) ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks
American College of Cardiology (ACC)/American Heart Association (AHA): **2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease[40] (2008)**	<u>Rheumatic Fever Prophylaxis</u> • Primary prevention of rheumatic heart disease: o Penicillin G benzathine IM once or penicillin V orally for 10 days o Erythromycin estolate or erythromycin ethylsuccinate orally for 10 days, or azithromycin orally for 5 days in patients who are allergic to penicillin • Secondary prevention of rheumatic fever: o Penicillin G benzathine IM every 4 weeks, or penicillin V orally twice daily, or sulfadiazine orally once daily o Erythromycin orally twice daily for patients who are allergic to penicillin <u>Endocarditis Prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with CHD o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30-60 minutes before procedure): o Oral: amoxicillin o Unable to take oral medications: Ampicillin, cefazolin or ceftriaxone o Allergic to penicillin or ampicillin (oral): cephalexin,

Clinical Guideline	Recommendation(s)
	clindamycin, or azithromycin o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis* o Penicillin G or ceftriaxone for 4 weeks o Ceftriaxone plus gentamicin for 2 weeks o Vancomycin for 4 weeks in patients allergic to penicillin • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin o Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2 weeks o Vancomycin for 4 weeks in patients allergic to penicillin • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin o Ampicillin for 4 to 6 weeks or penicillin G plus gentamicin for 4 to 6 weeks o Vancomycin plus gentamicin for 6 weeks in patients allergic to penicillin • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials o Oxacillin-susceptible strains ▪ Nafcillin or oxacillin for 6 weeks plus the optional addition of gentamicin for 3 to 5 days ▪ Cefazolin for 6 weeks with the optional addition of gentamicin in patients allergic to penicillin o Oxacillin-resistant strains ▪ Vancomycin for 6 weeks o Oxacillin-resistant strains • Therapy for prosthetic valve endocarditis caused by staphylococci o Oxacillin-susceptible strains ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks o Oxacillin-resistant strains ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks • Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms o Ceftriaxone for 4 weeks o Ampicillin-sulbactam for 4 weeks o Ciprofloxacin for 4 weeks • Therapy for culture-negative endocarditis including *Bartonella* endocarditis o Native valve ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for 4 to 6 weeks o Prosthetic valve (early; ≤1 year) ▪ Vancomycin for 6 weeks, plus gentamicin for 2 weeks, plus cefepime for 6 weeks, plus rifampin for 6 weeks o Prosthetic valve (late; >1 year) ▪ Suspected *Bartonella*, culture negative • Ceftriaxone for 6 weeks plus gentamicin with/without doxycycline for 6 weeks ▪ Documented *Bartonella*, culture positive

Clinical Guideline	Recommendation(s)
	• Doxycycline for 6 weeks plus gentamicin for 2 weeks
American Heart Association (AHA): **Infective Endocarditis: Diagnosis, Antimicrobial Therapy, and Management of Complications**[53] **(2005)**	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus bovis*: o Penicillin-susceptible strains ▪ Penicillin G or ceftriaxone for 4 weeks ▪ Penicillin G or ceftriaxone plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Penicillin-resistant strains: ▪ Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus bovis*: o Penicillin-susceptible strains ▪ Penicillin G or ceftriaxone for 6 weeks with or without gentamicin for 2 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Penicillin-resistant strains: ▪ Penicillin G or ceftriaxone for 6 weeks plus gentamicin for 6 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for 6 weeks with the option of adding gentamicin for 3-5 days ▪ For penicillin-allergic individuals: cefazolin for 6 weeks with the option of adding gentamicin for 3-5 days o Oxacillin-resistant strains ▪ Vancomycin for 6 weeks • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) o Oxacillin-resistant strains ▪ Vancomycin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) • Therapy for native valve or prosthetic valve enterococcal endocarditis o Strains susceptible to penicillin, gentamicin, and vancomycin: ▪ Ampicillin or penicillin G plus gentamicin for 4-6 weeks ▪ Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy)

Clinical Guideline	Recommendation(s)
	○ Strains susceptible to penicillin, streptomycin, and vancomycin and resistant to gentamicin: ▪ Ampicillin or penicillin G plus streptomycin for 4-6 weeks ▪ Vancomycin plus streptomycin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) ○ Strains resistant to penicillin and susceptible to aminoglycosides and vancomycin: ▪ β-lactamase–producing strain: • Ampicillin-sulbactam plus gentamicin for 6 weeks • Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for 6 weeks • Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms: ○ Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin-sulbactam or ciprofloxacin for 4-6 weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin, gatifloxacin, or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: ○ Native valve: ▪ Ampicillin-sulbactam plus gentamicin for 4-6 weeks ▪ Vancomycin plus gentamicin plus ciprofloxacin for 4-6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillins)
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines: Management of Encephalitis[120] (2008)**	Empirical Therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or trimethoprim-sulfamethoxazole is recommended • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; trimethoprim-sulfamethoxazole is an alternative in the penicillin-allergic patient • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered • *Tropheryma whipplei:* ceftriaxone, followed by either trimethoprim-sulfamethoxazole or cefixime, is recommended Rickettsioses and Ehrlichioses

Clinical Guideline	Recommendation(s)
	• *Anaplasma phagocytophilum:* doxycycline is recommended • *Ehrlichia chaffeensis:* doxycycline is recommended • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative Protozoa • *Acanthamoeba:* trimethoprim-sulfamethoxazole plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; trimethoprim-sulfamethoxazole alone and pyrimethamine plus either atovaquone, clarithromycin, azithromycin, or dapsone are alternatives • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended

European Federation of Neurological Societies (EFNS): **Guideline on the Management of Community-acquired Bacterial Meningitis[33] (2008)**	Empirical Therapy
	• Ceftriaxone 2 g every 12–24 hours or cefotaxime 2 g every 6–8 hours.
	• Alternative therapy: Meropenem 2 g every 8 hours or chloramphenicol 1 g every 6 hours.
	• If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg.
	• Ampicillin/amoxicillin 2 g every 4 hours if *Listeria* is suspected.
	Pathogen Specific Therapy
	• Penicillin-sensitive pneumococcal meningitis:
	  o Benzyl penicillin 250,000 U/kg/day, ampicillin/amoxicillin 2 g every 4 hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every 6–8 hours
	  o Alternative therapy: meropenem 2 g every 8 hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily
	• Pneumococcus with reduced susceptibility to penicillin or cephalosporins:
	  o Ceftriaxone or cefotaxime plus vancomycin ± rifampicin
	  o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin
	• Meningococcal meningitis:

Clinical Guideline	Recommendation(s)
	o Benzyl penicillin, ceftriaxone, or cefotaxime o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime o Alternative therapy: chloramphenicol–ampicillin/amoxicillin • Listerial meningitis: o Ampicillin or amoxicillin 2 g every 4 hours ± gentamicin 1–2 mg every 8 hours for the first 7– 10 days o Alternative therapy: trimethoprim–sulfamethoxazole 10–20 mg/kg every 6–12 hours or meropenem • *Staphylococcal* species: o Flucloxacillin 2 g every 4 hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem • Pseudomonal meningitis: o Meropenem ± gentamicin
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Bacterial Meningitis[34] (2004)**	Empiric Therapy • Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative CSF Gram stain result: • Age <1 month: ampicillin plus cefotaxime or ampicillin plus an aminoglycoside • Age 1–23 months: vancomycin plus a third-generation cephalosporin • Age 2-50 years: vancomycin plus a third-generation cephalosporin • Age >50 years: Vancomycin plus ampicillin plus a third-generation cephalosporin Specific Therapy • Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility. • *Streptococcus pneumoniae* o Penicillin MIC <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapies include ceftriaxone, cefotaxime, or chloramphenicol • *Neisseria meningitides* o Penicillin MIC <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapy includes ceftriaxone, cefotaxime or chloramphenicol • *Listeria monocytogenes* o Standard therapy includes ampicillin or penicillin G; alternative therapies include trimethoprim-sulfamethoxazole or meropenem • *Streptococcus agalactiae* o Standard therapy includes ampicillin or penicillin G; alternative therapies include ceftriaxone or cefotaxime • *Escherichia coli* and other enterobacteriaceae o Standard therapy includes a third-generation cephalosporin; alternative therapies include Aztreonam, fluoroquinolone, meropenem, trimethoprim-sulfamethoxazole or ampicillin • *Haemophilus influenzae* β-lactamase negative strains o Standard therapy includes ampicillin; alternative therapies

Clinical Guideline	Recommendation(s)
	include ceftriaxone, cefotaxime, cefepime, chloramphenicol or a fluoroquinolone • *Enterococcus* species ampicillin susceptible o Standard therapy includes ampicillin plus gentamicin

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections[35] (2005)**	Overview
	• Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first- or second-generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of methicillin-resistant S*taphylococcus aureus* (MRSA) strains.
	Animal Bites
	• Oral treatment options
	  o Amoxicillin/clavulanate is recommended.
	  o Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin.
	  o First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *P. multocida* and should be avoided.
	• Intravenous treatment options
	  o β-lactam/β-lactamase combinations, piperacillin/tazobactam, second-generation cephalosporins, and carbapenems.
	Animal Contact
	• Erysipeloid:
	  o For cutaneous infection, penicillin or amoxicillin for 7–10 days seems to be rational.
	Cellulitis
	• A large percentage of patients can receive oral medications from the start. Suitable agents include dicloxacillin, cephalexin, clindamycin, or erythromycin, unless streptococci or staphylococci.
	• For parenteral therapy, which is indicated for severely ill patients or for those unable to tolerate oral medications, reasonable choices include a penicillinase-resistant penicillin such as nafcillin, a first-generation cephalosporin such as cefazolin, or, for patients with life-threatening penicillin allergies, clindamycin or vancomycin.
	• In cases of uncomplicated cellulitis, 5 days of antibiotic treatment is as effective as a 10-day course.
	Erysipelas
	• Penicillin, given either parenterally or orally depending on clinical severity, is the treatment of choice.
	• If staphylococcal infection is suspected, a penicillinase-resistant semisynthetic penicillin or a first-generation cephalosporin should be selected.
	Human Bites
	• Clenched-fist injuries often require hospitalization and intravenous antimicrobial therapy with agents such as cefoxitin, ampicillin/sulbactam, ertapenem, or some combination that covers *S. aureus, Haemophilus* species, *E. corrodens,* and β-lactamase–producing anaerobes.
	Impetigo
	• The decision of how to treat impetigo depends on the number of lesions, their location (face, eyelid, or mouth), and the need to limit spread of infection to others.
	• Patients who have numerous lesions or who are not responding to topical agents should receive oral antimicrobials effective against both *S. aureus* and *S. pyogenes.*

Clinical Guideline	Recommendation(s)
	• Because *S. aureus* currently accounts for most cases of bullous impetigo, as well as for a substantial portion of nonbullous infections, penicillinase-resistant penicillins or first generation cephalosporins are preferred. • Additional therapies include clindamycin or amoxicillin/clavulanate. Necrotizing Infections • Antimicrobial therapy must be directed at the pathogens and used in appropriate doses until repeated operative procedures are no longer needed, the patient has demonstrated obvious clinical improvement, and fever has been absent for 48–72 h. • The best choice of antibiotics for community-acquired mixed infections is a combination of ampicillin-sulbactam plus clindamycin plus ciprofloxacin. The carbapenems, or a combination of cefotaxime plus metronidazole or clindamycin, are also appropriate. In cases of penicillin allergy, alternatives include clindamycin or metronidazole plus an aminoglycoside or fluoroquinolone. • *S aureus* infection, often associated with pyomyositis, should be treated with nafcillin, oxacillin, or cefazolin. Vancomycin should be reserved for resistant strains or can be used in cases of severe penicillin allergy, as well as linezolid, quinupristin-dalfopristin or daptomycin. Clindamycin is limited by its potential of cross-resistance. Surgical Site Infections • If there is minimal surrounding evidence of invasive infection (<5 cm of erythema and induration), and if the patient has minimal systemic signs of infection (a temperature of <38.5°C and a pulse rate of <100 beats/min), antibiotics are unnecessary. • For patients with a temperature of >38.5°C or a pulse rate of >100 beats/min, a short course of antibiotics, usually for a duration of 24–48 h, may be indicated. The antibiotic choice is usually empirical but can be supported by findings of Gram stain and results of culture of the wound contents. • For intestinal or genital tract surgical site infections, single agents such as cefoxitin, ceftizoxime, ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam, or carbapenems are indicated. In cases where facultative and aerobic activity is desired, fluoroquinolones, third-generation cephalosporins, aztreonam, or aminoglycosides are recommended. When anaerobic activity is desired, appropriate treatment includes clindamycin, metronidazole, chloramphenicol or a penicillin agent plus a β-lactamase inhibitor. • In axillary or perineum surgical site infections, cefoxitin, ampicillin-sulbactam or agents indicated for intestinal and genital sites are appropriate.
Infectious Diseases Society of America (IDSA): **Diagnosis and Treatment of Diabetic Foot Infections**[117] **(2004)**	• Empirical antibiotic regimens should be based on the clinical severity of the infection. • Current clinical data does not allow for the recommendation of any specific antibiotic regimen for diabetic foot infections (DFIs). • Suggested agents are derived from available published clinical trials and expert experience. • Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have US Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid is currently specifically approved for diabetic foot infections.

Clinical Guideline	Recommendation(s)
	• Suggested empirical antibiotic regimens for mild infections: dicloxacillin, clindamycin, cephalexin, trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, levofloxacin • Suggested empirical antibiotic regimens for moderate infections: trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, levofloxacin, cefoxitin, ceftriaxone, ampicillin/sulbactam, linezolid (with or without aztreonam), daptomycin (with or without aztreonam), ertapenem, cefuroxime (with or without metronidazole), ticarcillin/clavulanate, piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin • Suggested empirical antibiotic regimens for severe infections: piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin, imipenem-cilastatin, vancomycin and ceftazidime (with or without metronidazole)
American College of Gastroenterology (ACG): **Guideline on the Management of *Helicobacter pylori* Infection**[36] **(2007)**	• The recommended primary therapies for H. pylori infection include: a PPI, clarithromycin, and amoxicillin, or metronidazole (clarithromycin-based triple therapy) for 14 days or a PPI or H2RA, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10–14 days.
Canadian Helicobacter Study Group: **Update on the Management of *Helicobacter pylori***[37] **(2004)**	• A quadruple combination of a PPI, bismuth, tetracycline, and metronidazole for 10-14 days can be considered first-line therapy for the eradication of *H. pylori*. • Eradication rates with the recommended quadruple therapy are comparable with those achieved with PPI-based triple therapy regimens in patients who adhere to the protocol. Given the lower number of tablets and twice daily dosing, in practice, PPI-based triple therapy may be the first choice.
European *Helicobacter pylori* Study Group: **Current Concepts in the Management of *H. pylori* Infection–The Maastricht 2-2000 Consensus Report**[38] **(2002)**	• First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole. • Second-line therapy should use quadruple therapy with a PPI, bismuth, metronidazole, and tetracycline. • When bismuth is not available, second-line therapy should be triple therapy with a proton-pump inhibitor.
Canadian Dyspepsia Working Group: **An Evidence-Based Approach to the Management of Uninvestigated Dyspepsia in the Era of *Helicobacter pylori***[39] **(2000)**	• First-line eradication therapies for *H. pylori* are triple therapies of a PPI plus amoxicillin plus clarithromycin (PPI + AC), or a PPI plus metronidazole plus clarithromycin (PPI + MC), twice daily for 1 week; or ranitidine bismuth citrate plus either AC or MC. • If the first eradication therapy has failed, the action recommended by the Canadian *Helicobacter pylori* Consensus Conference is to use a different first-line therapy than that used initially (e.g., switch from PPI + AC to PPI + MC).

Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines**[41] **(2010)**	<u>Primary and Secondary Syphilis</u>
	• Recommended regimen for adults:
	  o Benzathine penicillin G 2.4 million units IM in a single dose
	• Recommended regimen for infants and children:
	  o Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose
	<u>Early Latent Syphilis</u>
	• Recommended regimens for adults:
	  o Benzathine penicillin G 2.4 million units IM in a single dose
	• Recommended regimens for children:
	  o Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose

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	Late Latent Syphilis or Latent Syphilis of Unknown Duration
	• Recommended regimens for adults:
	  o Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals
	• Recommended regimens for children:
	  o Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units, administered as 3 doses at 1-week intervals
	Tertiary Syphilis
	• Recommended regimen:
	  o Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals
	Neurosyphilis
	• Recommended regimen:
	  o Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days
	• Alternative regimen:
	  o Procaine penicillin 2.4 million units IM once daily plus probenecid 500 mg orally four times a day, both for 10–14 days
	Pelvic Inflammatory Disease
	• Recommended parenteral regimen A:
	  o Cefotetan 2 g IV every 12 hours
	  o Cefoxitin 2 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours
	• Recommended parenteral regimen B:
	  o Clindamycin 900 mg IV every 8 hours plus gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) can be substituted.
	• Alternative parenteral regimens:
	  o Ampicillin/Sulbactam 3 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours
	• Recommended oral regimen:
	  o Ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
	  o Cefoxitin 2 g IM in a single dose and probenecid, 1 g orally administered concurrently in a single dose, plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
	  o Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days

Infectious Diseases Society of America (IDSA)/European Society for Microbiology and Infectious Diseases (ESCMID): **International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women[44] (2010)**	Acute Uncomplicated Bacterial Cystitis • Nitrofurantoin monohydrate/macrocrystals (100 mg BID for 5 days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage. • Trimethoprim-sulfamethoxazole (160/800 mg BID for 3 days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible.

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	• Fosfomycin (3 g in a single dose) is an appropriate choice for therapy where it's available due to minimal resistance and propensity for collateral damage, but it appears to be less effective compared to standard short-course regimens. • Ofloxacin, ciprofloxacin and levofloxacin are highly efficacious in 3-day regimens, but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis. • β-lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in 3-7 day regimens are appropriate choices for therapy when other recommended agents cannot be used. Other β-lactams, such as cephalexin are less well studied, but may also be appropriate in certain settings. The β-lactams are generally less effective and have more adverse effects compared with other UTI antimicrobials. For these reasons, β-lactams should be used with caution for uncomplicated cystitis. • Amoxicillin or ampicillin should not be used for empirical treatment given the relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. <u>Acute Pyelonephritis</u> • Oral ciprofloxacin (500 mg BID) for 7 days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice when resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. A long-acting antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) may replace the initial one time IV ciprofloxacin, and is recommended if the fluoroquinolone resistance is thought to exceed 10%. • Once-daily fluoroquinolones (ciprofloxacin 100 mg extended-release for 7 days, levofloxacin 750 mg for 5 days) is an appropriate choice when resistance to community uropathogens is not known to exceed 10%. If resistance is thought to exceed 10%, an initial intravenous dose of long-acting parenteral antimicrobial (ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral trimethoprim/sulfamethoxazole (160/800 mg BID) for 14 days is an appropriate choice of therapy when the uropathogen is known to be susceptible. If susceptibility is unknown, an initial IV dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral β-lactams are less effective than other available agents for the treatment of pyelonephritis. If an oral β-lactam is used, an initial IV dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • For patients requiring hospitalization, initial treatment with an intravenous antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin with or without an aminoglycoside, or a carbapenem is recommended. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results.

American College of Obstetricians and Gynecologists (ACOG): **Treatment of Urinary Tract Infections in Nonpregnant Women[43] (2008)**	• For uncomplicated acute bacterial cystitis, recommended treatment regimens are as follows:
	  o Trimethoprim–sulfamethoxazole: 1 tablet (160 mg trimethoprim–800 mg sulfamethoxazole) twice daily for 3 days.
	  o Trimethoprim 100 mg twice daily for 3 days.

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	o Ciprofloxacin 250 mg twice daily for 3 days, levofloxacin 250 mg once daily for 3 days, norfloxacin 400 mg twice daily for 3 days, or gatifloxacin 200 mg, once daily for 3 days. o Nitrofurantoin macrocrystals 50 to 100 mg 4 times daily for 7 days, or nitrofurantoin monohydrate 100 mg twice daily for 7 days. o Fosfomycin tromethamine, 3-g dose (powder) single dose.
American Academy of Pediatrics (AAP)/American Academy of Family Physicians (AAFP): **Diagnosis and Management of Acute Otitis Media**[45] **(2004)**	Observation Option • Observation without use of antibacterial agents in a child with uncomplicated acute otitis media (AOM) is an option for selected children based on diagnostic certainty, age, illness severity, and assurance of follow-up. The "observation option" for AOM refers to deferring antibacterial treatment of selected children for 48 to 72 hours and limiting management to symptomatic relief. This option should be limited to otherwise healthy children 6 months to 2 years of age with non-severe illness at presentation and an uncertain diagnosis and to children 2 years of age and older without severe symptoms at presentation or with an uncertain diagnosis. Antibacterial Options - Temperature <39°C Without Severe Otalgia • For the initial treatment of otitis media, the recommended agent is amoxicillin 80-90 mg/kg/day. • For treatment failures at 48-72 hours after initial management with observation option, the recommended agent is amoxicillin 80-90 mg/kg/day. • For treatment failures at 48-72 hours after initial management with antibacterial agents, the recommended agent is amoxicillin-clavulanate. Antibacterial Options - Temperature ≥39°C and/or Severe Otalgia • For the initial treatment of otitis media, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48-72 hours after initial management with observation option, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48-72 hours after initial management with antibacterial agents, the recommended agent is ceftriaxone for 3 days.
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Group A Streptococcal Pharyngitis**[48] **(2002)**	• Patients with acute streptococcal pharyngitis should receive therapy with an antimicrobial agent in a dose and for a duration that is likely to eradicate the infecting organism from the pharynx. • Penicillin remains the agent of choice because of its proven efficacy, safety, and narrow spectrum. • Amoxicillin is often used in place of oral penicillin V to treat young children; the efficacy appears to be equal. This choice is primarily related to acceptance of the taste of the suspension. • Intramuscular administration of benzathine penicillin G is preferred for patients who are unlikely to complete a full 10- day course of oral therapy. • Most oral antibiotic therapy must be administered for the conventional 10 days to achieve maximal rates of pharyngeal eradication of group A streptococci. • When multiple episodes occur over the course of months or years, it may be difficult to differentiate viral pharyngitis in a *Streptococcus* carrier from true group A streptococcal pharyngitis. Therapy with certain antimicrobial agents, such as clindamycin and amoxicillin-clavulanate, may be beneficial, because they have been shown to yield high rates of eradication of streptococci from the pharynx under these particular circumstances.

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American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF): **Clinical Practice Guideline: Adult Sinusitis**[42] **(2007)**	Symptomatic Relief of Viral Rhinosinusitis (VRS) • Management of VRS is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Topical or systemic decongestants may offer additional symptomatic relief. • Antihistamines have been used to treat VRS due to their drying effect; however, no studies have been published that assess the impact of antihistamines specifically on VRS outcomes. Adverse effects of antihistamines, especially first-generation H_1-antagonists, include drowsiness, behavioral changes, and impaired mucus transport in the nose and sinuses because of drying. Symptomatic Relief of Acute Bacterial Rhinosinusitis (ABRS) • Symptomatic treatments for ABRS include decongestants, corticosteroids, saline irrigation, and mucolytics. None of these products have been approved by the FDA for use in acute rhinosinusitis, and few have data from controlled clinical studies supporting this use. • Antihistamines have no role in the symptomatic relief of ABRS in nonatopic patients. There are no studies that support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. • Antihistamines may be considered in patients with ABRS whose symptoms suggest a significant allergic component. Watchful Waiting for Acute Bacterial Rhinosinusitis (ABRS) • Observation without use of antibiotics is an option for selected adults with uncomplicated ABRS who have mild illness (mild pain and temperature <38.3°C or 101°F). Choice of Antibiotic for Acute Bacterial Rhinosinusitis (ABRS) • If a decision is made to treat ABRS with an antibiotic, the clinician should prescribe amoxicillin as first-line therapy for most adults. Treatment Failure for Acute Bacterial Rhinosinusitis (ABRS) • If the patient worsens or fails to improve with the initial management option by 7 days after diagnosis, the clinician should reassess the patient to confirm ABRS, exclude other causes of illness, and detect complications. • If ABRS is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI): **The Diagnosis and Management of Sinusitis: An Updated Practice Parameter**[46] **(2005)**	• Antibiotics are the primary therapy for bacterial sinusitis. • The most common bacteria observed in acute sinusitis, recurrent acute sinusitis, and acute exacerbations of chronic sinusitis are *S pneumoniae*, *H influenzae*, and *M catarrhalis*. • Choice of antibiotic should be based on predicted effectiveness and side effects. • Amoxicillin is a reasonable initial antibiotic choice in both children and adults with uncomplicated disease. It is generally effective and side effects are rare. A substantial drawback of amoxicillin is lack of effectiveness against β-lactamase–producing strains. This can be overcome by the addition of potassium clavulanate, which can inhibit the β-lactamase enzymes. Such a combination of amoxicillin–potassium clavulanate is typically effective against most β-lactamase–producing *H influenzae*, *M catarrhalis*, *S aureus*, and anaerobic bacteria. • For patients allergic to or intolerant of amoxicillin, alternatives include

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	cephalosporins, macrolides, or quinolones. • Acute sinusitis generally responds to treatment for 10 to 14 days. Some physicians continue treatment for 7 days after the patient is well to ensure complete eradication of the organism and prevent relapse. • A reasonable approach would be to start the patient on amoxicillin for 3 to 5 days and determine whether the signs and symptoms are improving. If the patients symptoms are improving, continue this treatment until the patient is well for 7 days (generally a 10- to 14-day course). If after 3 to 5 days the patient has not shown improvement, switch to a different antibiotic, such as high-dose amoxicillin-clavulanate or cefuroxime axetil.
American Academy of Pediatrics (AAP): **Clinical Practice Guideline: Management of Sinusitis**[47] **(2001)**	• Antibiotics are recommended for the management of acute bacterial sinusitis to achieve a more rapid clinical cure. • The principle bacterial pathogens in bacterial sinusitis are *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis.* • For children younger than 2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in degree of severity, who do not attend day care, and have not recently been treated with an antimicrobial, amoxicillin is recommended. • If patients do not improve while receiving the usual dose of amoxicillin (45 mg/kg/d), have recently been treated with an antimicrobial, have an illness that is moderate or more severe, or attend day care, therapy should be initiated with high-dose amoxicillin-clavulanate (80–90 mg/kg/d of amoxicillin component, with 6.4 mg/kg/d of clavulanate in 2 divided doses).
Working Group on Civilian Biodefense: **Anthrax as a Biological Weapon, Updated Recommendations for Management**[51] **(2002)**	<u>Inhalation Anthrax in the Contained Casualty Setting - Adults</u> • Ciprofloxacin 400 mg IV every 12 hours initially, then 500 mg by mouth twice daily when clinically appropriate OR • Doxycycline 100 mg IV every 12 hours initially with either one or two of the following: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and/or clarithromycin. Switch to 100 mg by mouth twice daily when clinically appropriate. <u>Inhalation Anthrax in the Contained Casualty Setting - Children</u> • Ciprofloxacin 10-15 mg/kg every 12 hours IV, then 10-15 mg/kg by mouth every 12 hours when clinically appropriate OR • Doxycycline (if ≤45 kg–2.2 mg/kg IV; if > 45 kg–100 mg IV) every 12 hours initially with either one or two of the following: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and/or clarithromycin. Switch to oral therapy when clinically appropriate using same IV dose. <u>Inhalation Anthrax in a Mass Casualty Setting - Adults</u> • Recommended treatment: ciprofloxacin 500 mg by mouth every 12 hours • Alternative treatment option: doxycycline 100 mg by mouth every 12 hours or amoxicillin 500 mg by mouth every 8 hours <u>Inhalation Anthrax in a Mass Casualty Setting - Children</u> • Recommended treatment: ciprofloxacin 10-15 mg/kg by mouth every 12 hours • Alternative treatment option: amoxicillin 500 mg by mouth every 8 hours (weight ≥20 kg) or amoxicillin 40 mg/kg by mouth every 8 hours (weight <20 kg) <u>Inhalation Anthrax in a Mass Casualty Setting – Pregnant Women</u> • Recommended treatment: ciprofloxacin 500 mg by mouth every 12 hours

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	• Alternative treatment option: amoxicillin 500 mg every 8 hours

Global Initiative for Chronic Obstructive Lung Disease (GOLD): **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[56] (2010)**	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in COPD.
	• There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful.
	• Based on current available evidence, antibiotics should be given to:
	  o Patients with exacerbations of COPD with the following three cardinal symptoms: dyspnea, sputum volume, and sputum purulence.
	  o Patients with exacerbations of COPD with two of the cardinal symptoms, if the increased purulence of sputum is one of the two symptoms.
	  o Patients with a severe exacerbation of COPD that requires mechanical ventilation (invasive or noninvasive).
	• Antibiotic treatment in exacerbations of COPD:
	  o Group A (mild exacerbation; no risk factors for poor outcome)
	  ▪ Recommended oral treatment: β-lactam (penicillin, ampicillin, amoxicillin), tetracycline, or trimethoprim-sulfamethoxazole
	  ▪ Alternative oral treatment: β-lactam/β-lactamase inhibitor, macrolides, second or third generation cephalosporin, or ketolides
	  o Group B (moderate exacerbation with risk factor(s) for poor outcome)
	  ▪ Recommended oral treatment: β-lactam/β-lactamase inhibitor
	  ▪ Alternative oral treatment: fluoroquinolones (gemifloxacin, levofloxacin, moxifloxacin)
	  ▪ Parenteral treatment: β-lactam/β-lactamase inhibitor, second or third generation cephalosporin, or fluoroquinolones (levofloxacin, moxifloxacin)
	  o Group C (severe exacerbation with risk factors for *P. aeruginosa* infection)
	  ▪ Recommended oral treatment: fluoroquinolones (ciprofloxacin, levofloxacin)
	  ▪ Parenteral treatment: fluoroquinolones (ciprofloxacin, levofloxacin) or β-lactam with *P. aeruginosa* activity

Infectious Diseases Society of America (IDSA): **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age[118] (2011)**	<u>Outpatient Treatment</u>
	• Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia (CAP), because viral pathogens are responsible for the great majority of clinical disease.
	• Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate CAP suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*.
	• For patients allergic to amoxicillin, the following agents are considered alternative treatment options:
	  o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil)
	  o Levofloxacin (oral therapy)
	  o Linezolid (oral therapy)
	• Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an

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	outpatient setting with findings compatible with CAP caused by atypical pathogens. Inpatient Treatment • Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with CAP when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *S. pneumoniae*. • Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. • Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *M. pneumoniae* and *C. pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *S. aureus*.

Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS): **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults**[49] **(2007)**	Empirical Antimicrobial Therapy
	• Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.
	• Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.
	• Outpatient treatment
	  o Previously healthy and no risk factors for drug-resistant *S. pneumoniae* (DRSP) infection:
	  ▪ Macrolide (azithromycin, clarithromycin, or erythromycin)
	  ▪ Doxycycline
	  o Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected); or other risks for DRSP infection:
	  ▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin)
	  ▪ β-lactam plus a macrolide (high-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide.)
	  o In regions with a high rate of infection with high-level macrolide-resistant *S. pneumoniae,* consider the use of alternative agents listed above for any patient, including those without comorbidities.
	• Inpatient, non-ICU treatment
	  o Respiratory fluoroquinolone

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	o β-lactam plus a macrolide (preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients). • Inpatient, ICU treatment o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended.) o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam). o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.
American College of Chest Physicians (ACCP): **Management of Community-Acquired Pneumonia in the Home: An American College of Chest Physicians Clinical Position Statement[50] (2005)**	• Antibiotic choice and route of administration are central to an appropriate in-home treatment plan. The oral route is recommended if the patient can tolerate it, and if the availability and activity of the agent are adequate. • Although treatment is facilitated if the etiologic agent is known (pathogen-directed treatment for CAP is provided in the IDSA guidelines), most outpatient treatment is empiric. • The use of a macrolide, doxycycline, or fluoroquinolone agent, as recommended both by the IDSA and the ATS guidelines, may be appropriate empiric outpatient treatment for low-risk patients (i.e., otherwise young healthy individuals). Alternatives to these agents in low-risk patients are amoxicillin/clavulanate and some second-generation cephalosporins (e.g., cefuroxime, cefpodoxime, or cefprozil). • The IDSA and ATS recommendations generally agree that a patient who is at high risk either because of complicated comorbidities or extensive prior antibiotic use may be a candidate for treatment with either a β-lactam/macrolide combination or a antipneumococcal fluoroquinolone. • Double therapy with either a β-lactam/macrolide combination or a β-lactam/ antipneumococcal fluoroquinolone should be considered in patients who would normally be considered for ICU admission but have chosen to remain in the home.
American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA): **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia[115] (2005)**	• Select an initial empiric therapy based on the absence or presence of risk factors for multidrug-resistant (MDR) pathogens. These risk factors include prolonged duration of hospitalization (5 days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy. • Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins. • In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of

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	inappropriate therapy and can predispose to resistance to that same class of antibiotics.
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for MDR pathogens, early onset, and any disease severity:
	  o Ceftriaxone OR
	  o Levofloxacin, moxifloxacin, ciprofloxacin OR
	  o Ampicillin/sulbactam OR
	  o Ertapenem
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for MDR pathogens and all disease severity – combination antibiotic therapy is recommended as follows:
	  o Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if MRSA risk factors are present or there is a high incidence locally.

Infectious Diseases Society of America (IDSA): **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children[54] (2010)**	Community-Acquired Infection in Adults: Mild to Moderate Severity • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*E. Coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. Community-Acquired Infection in Adults: High Severity • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *E. coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E. coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended.

Clinical Guideline	Recommendation(s)
	• In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended. • Use of agents effective against MRSA or yeast is not recommended in the absence of evidence of infection due to such organisms. <u>Community-Acquired Infection in Pediatric Patients:</u> • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected MRSA or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. <u>Health Care-Associated Infection:</u> • Therapy should be based on microbiologic results. To achieve empiric coverage, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. <u>Cholecystitis and Cholangitis:</u> • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.
Infectious Diseases Society of America (IDSA): **Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis[55] (2006)**	• Doxycycline, amoxicillin or cefuroxime axetil for 14 days is recommended for the treatment of adult patients with early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of specific neurologic manifestations (see Lyme meningitis, below) or advanced atrioventricular heart block. • Each of these antimicrobial agents has been shown to be highly effective for the treatment of erythema migrans and associated symptoms in prospective studies. • Doxycycline has the advantage of being effective for treatment of

Clinical Guideline	Recommendation(s)
	HGA (but not for babesiosis), which may occur simultaneously with early Lyme disease.
Infectious Diseases Society of America (IDSA): **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus*[119] (2011)**	Skin and Soft-Tissue Infections (SSTIs) • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired (CA) MRSA is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for CA-MRSA is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of CA-MRSA in outpatients with SSTI, oral antibiotic options include the following: clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and CA-MRSA is desired, options include the following: clindamycin alone or TMP-SMX or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of SSTIs is not recommended. • For hospitalized patients with complicated SSTIs, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for MRSA should be considered pending culture data. Options include the following: vancomycin intravenous (IV), linezolid oral (PO) or IV, daptomycin IV, telavancin IV, and clindamycin IV or PO. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to MRSA-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with cSSTIs, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin IV is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative. MRSA Bacteremia and Infective Endocarditis (Native Valve) • For adults with uncomplicated bacteremia, vancomycin or daptomycin IV for at least 2 weeks is recommended. For complicated bacteremia, 4–6 weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, IV vancomycin or daptomycin

Clinical Guideline	Recommendation(s)

	for 6 weeks is recommended.
	• Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis.
	<u>MRSA Bacteremia and Infective Endocarditis (Prosthetic Valve)</u>
	• IV vancomycin plus rifampin PO/IV for at least 6 weeks plus gentamicin IV for 2 weeks.
	• In children, vancomycin IV is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from 2 to 6 weeks depending on source, presence of endovascular infection, and metastatic foci of infection.
	• Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin IV may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus.
	• Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis.
	<u>Management of MRSA Pneumonia</u>
	• For hospitalized patients with severe community-acquired pneumonia, empirical therapy for MRSA is recommended pending sputum and/or blood culture results.
	• For health care–associated MRSA (HA-MRSA) or CA-MRSA pneumonia, IV vancomycin or linezolid PO/IV or clindamycin PO/IV, if the strain is susceptible, is recommended for 7–21 days, depending on the extent of infection.
	• In children, IV vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin IV can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative.
	<u>Management of MRSA Bone and Joint Infections</u>
	• Antibiotics available for parenteral administration include IV vancomycin and daptomycin.
	• Some antibiotic options with parenteral and oral routes of administration include the following: TMP-SMX in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.
	• A minimum 8-week course is recommended. Some experts suggest an additional 1–3 months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with TMP-SMX, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities.
	• For septic arthritis, refer to antibiotic choices for osteomyelitis. A 3 to 4-week course of therapy is suggested.
	<u>Management of MRSA Infections of the CNS</u>
	• Meningitis
	  o IV vancomycin for 2 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid or TMP-SMX.
	  o For CNS shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid (CSF) cultures are repeatedly negative.

Clinical Guideline	Recommendation(s)

	• Brain abscess, subdural empyema, spinal epidural abscess
	  o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and TMP-SMX.
	• Septic thrombosis of cavernous or dural venous sinus
	  o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and TMP-SMX.
	  o IV vancomycin is recommended in children.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the penicillins are noted in Tables 5-6. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 5. FDA-Approved Indications for the Penicillins (Drugs A-O)[1-12]

Indication	Amoxicillin	Amoxicillin/ Clavulanate	Ampicillin	Ampicillin/ Sulbactam	Dicloxacillin	Nafcillin	Oxacillin
Central Nervous System Infections							
Meningitis			✔ ‡§				
Dermatological Infections							
Skin and skin-structure infections	✔ §	✔ §		✔			
Gastrointestinal Infections							
Gastrointestinal infections			✔ ‡§				
Treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or 1 year history of a duodenal ulcer) to eradicate *H. pylori* (in combination with clarithromycin plus lansoprazole as triple therapy)	✔ §						
Treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or 1 year history of a duodenal ulcer) who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected (in combination with lansoprazole delayed-release capsules as dual therapy)	✔ §						
Genitourinary Infections							
Genitourinary infections	✔ §		✔ §				
Gonorrhea	✔ §		✔ §				
Gynecologic infections				✔			
Urinary tract infections		✔ §	✔ ‡				
Respiratory Infections							
Ear, nose, and throat infections	✔ §						
Otitis media		✔ §					
Pharyngitis and/or tonsillitis	✔ †						
Pneumonia (community-acquired)		✔ †					
Respiratory tract infections			✔ ‡§				
Respiratory tract infections (lower)	✔ §	✔ §					
Sinusitis		✔ §†					

Indication	Amoxicillin	Amoxicillin/ Clavulanate	Ampicillin	Ampicillin/ Sulbactam	Dicloxacillin	Nafcillin	Oxacillin
Miscellaneous Infections							
Endocarditis			✔ ‡				
Intra-abdominal infections				✔			
Penicillinase-producing staphylococci					✔	✔	✔
Septicemia			✔ ‡				

†Extended-release oral formulations
§Immediate-release oral formulations
‡Injection formulation

Table 6. FDA-Approved Indications for the Penicillins (Drugs P-T)[1-12]

Indication	Penicillin G Benzathine	Penicillin G Benzathine/ Penicillin G Procaine	Penicillin G Potassium	Penicillin G Sodium	Penicillin G Procaine	Penicillin V Potassium	Piperacillin/ Tazobactam	Ticarcillin/ Clavulanate
Central Nervous System Infections								
Chorea (prophylaxis)	✔					✔		
Meningitis			✔	✔				
Neurosyphilis				✔				
Dermatological Infections								
Abscesses (cutaneous)							✔	
Bejel	✔				✔			
Cellulitis							✔	
Diabetic foot infections							✔	
Erysipelas		✔			✔	✔		
Erysipeloid					✔			
Gas gangrene				✔				
Pinta	✔				✔			
Skin and skin-structure infections		✔			✔	✔	✔	✔
Yaws	✔				✔			
Genitourinary Infections								
Endometritis							✔	✔
Genitourinary infections			✔	✔				
Gonococcal infections				✔				
Pelvic inflammatory disease							✔	
Syphilis	✔		✔	✔	✔			
Urinary tract infections								✔
Respiratory Infections								
Diphtheria (prevention of carrier state)			✔		✔			
Diphtheria (adjunct to antitoxin and prevention of carrier state)				✔				

Indication	Penicillin G Benzathine	Penicillin G Benzathine/ Penicillin G Procaine	Penicillin G Potassium	Penicillin G Sodium	Penicillin G Procaine	Penicillin V Potassium	Piperacillin/ Tazobactam	Ticarcillin/ Clavulanate
Otitis media		✔				✔		
Pharyngitis and/or tonsillitis					✔	✔		
Pneumonia		✔	✔	✔	✔			
Pneumonia (community-acquired)							✔	
Pneumonia (nosocomial)							✔	
Respiratory tract infections					✔	✔		
Respiratory tract infections (lower)			✔	✔				✔
Respiratory tract infections (upper)	✔	✔			✔	✔		
Vincent's infection			✔	✔	✔	✔		
Miscellaneous Infections								
Actinomycosis			✔	✔				
Anthrax			✔	✔	✔			
Appendicitis							✔	
Bacteremia			✔	✔				
Bone and/or joint infections								✔
Botulism (adjunct to antitoxin)				✔				
Clostridial infections			✔	✔				
Empyema			✔	✔				
Endocarditis			✔	✔	✔	✔		
Haverhill fever				✔				
Listeria infections			✔	✔				
Pasteurella infections			✔	✔				
Pericarditis			✔	✔				
Peritonitis							✔	✔
Rat-bite fever			✔	✔	✔			
Rheumatic fever (prophylaxis)	✔					✔		
Scarlet fever		✔			✔	✔		
Septicemia				✔				✔
Staphylococcal infections			✔					
Streptococcal infections			✔		✔			
Tetanus (adjunct)				✔				

IV. Pharmacokinetics

The pharmacokinetic parameters of the penicillins are listed in Table 7.

Table 7. Pharmacokinetic Parameters of the Penicillins[1-12]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Amoxicillin	89	15-25	Not reported	Renal (50-70)	1.0-1.3
Amoxicillin and clavulanate	Well absorbed	A: 18 C: 25	C: Liver	A: Renal (50-70) C: Renal (25-40)	A: 1.0-1.3 C: 1.0
Ampicillin	50	20	Not reported	Renal (40-92) Bile	1.0-1.9
Ampicillin and sulbactam	A: 92 (IM) S: 100 (IM)	A: 17-28 S: 38	Not reported	Renal (75-85)	A: 1.0-1.8 S: 1.0-1.3
Dicloxacillin	60-80	88-98	Not reported	Renal (35-90)	0.7
Nafcillin	N/A	87-90	Liver (60-70)	Renal (31-38) Bile (8)	0.5-1.0
Oxacillin	N/A	94	Liver (75)	Renal (39-66)	23-45 min
Penicillin G	Oral: <30 IM: 72	65	Liver (30)	Renal (79-85)	20-50 min
Penicillin G benzathine and penicillin G procaine	IM: slowly	30-60	Liver (30)	Renal (60-90)	20-30 min
Penicillin V	25-60	60-80	Not reported	Renal (20-40) Feces (32)	30-40 min
Piperacillin and tazobactam	IM: 71	30	Liver	P: Renal (68) T: Renal (80)	0.7-1.2
Ticarcillin and clavulanate	N/A	T: 45 C: 25	Liver, extensive	T: Renal (60-77) C: Renal (35-45)	T: 66-68 min C: 64-91 min

V. Drug Interactions

Significant drug interactions with the penicillins are listed in Table 8.

Table 8. Significant Drug Interactions with the Penicillins[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Penicillins	1	Methotrexate	Penicillins may increase the serum concentrations and pharmacologic effects of methotrexate. Toxicity may occur.
Dicloxacillin, nafcillin	2	Anticoagulants	Plasma concentrations and anticoagulant effects of anticoagulants may be decreased by these agents.
Penicillin G procaine	2	Succinylcholine	Neuromuscular blocking effects of succinylcholine may be increased by penicillin G procaine
Penicillins	2	Tetracyclines	The antimicrobial effectiveness of penicillins may be decreased by tetracyclines.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the penicillins are listed in Tables 9-10. The boxed warning for penicillin G benzathine and penicillin G benzathine/penicillin G procaine is listed in Table 11.

Table 9. Adverse Drug Events (%) Reported with the Penicillins (Drugs A-O)[1-12]

Adverse Events	Amoxicillin	Amoxicillin/ Clavulanate	Ampicillin	Ampicillin/ Sulbactam	Dicloxacillin	Nafcillin	Oxacillin
Cardiovascular							
Chest pain	-	-	-	<1	-	-	-
Central Nervous System							
Agitation	✔	-	-	-	-	-	-
Anxiety	✔	-	-	-	-	-	-
Behavioral changes	✔	-	-	-	-	-	-
Chills	-	-	-	<1	-	-	-
Confusion	✔	-	-	-	-	-	-
Dizziness	✔	-	-	-	-	-	-
Fatigue	-	-	-	<1	-	-	-
Fever	-	-	✔	-	-	-	✔
Headache	✔	✔	-	<1	-	-	-
Hyperactivity	✔	-	-	-	-	-	-
Insomnia	✔	-	-	-	-	-	-
Neurotoxicity	-	-	-	-	-	✔	-
Penicillin encephalopathy	-	-	✔	-	-	-	-
Seizure	✔	-	✔	<1	<1	-	-
Dermatologic							
Acute exanthematous pustulosis	✔	-	-	-	-	-	-
Diaper rash	-	✔	-	-	-	-	-
Erythema	-	-	-	<1	-	-	-
Erythema multiforme	✔	-	✔	-	-	-	-
Erythematous maculopapular rash	✔	-	-	-	-	-	-
Exfoliative dermatitis	✔	-	✔	-	-	-	-
Facial swelling	-	-	-	<1	-	-	-
Rash	-	1-10	✔	1-10	<1	-	✔
Stevens-Johnson syndrome	✔	-	-	-	-	-	-
Toxic epidermal necrolysis	✔	-	-	-	-	-	-
Urticaria	✔	1-10	✔	<1	-	-	-
Gastrointestinal							
Abdominal distension	-	-	-	<1	-	-	-

Adverse Events	Amoxicillin	Amoxicillin/ Clavulanate	Ampicillin	Ampicillin/ Sulbactam	Dicloxacillin	Nafcillin	Oxacillin
Abdominal pain	-	1-10	-	-	1-10	-	-
Black hairy tongue	✔	-	✔	<1	-	-	-
Diarrhea	✔	3-34	✔	1-10	1-10	-	✔
Enterocolitis	-	-	✔	-	-	-	-
Flatulence	-	✔	-	<1	-	-	-
Glossitis	-	-	✔	<1	-	-	-
Hemorrhagic colitis	✔	-	-	-	-	-	-
Loose stools	-	✔	-	-	-	-	-
Mucocutaneous candidiasis	✔	-	-	-	-	-	-
Mucosal bleeding	-	-	-	<1	-	-	-
Nausea	✔	1-10	✔	<1	1-10	-	✔
Pseudomembranous colitis	✔	-	✔	<1	<1	✔	-
Sore mouth or tongue	-	-	✔	-	-	-	-
Stomatitis	-	-	✔	-	-	-	-
Throat tightness	-	-	-	<1	-	-	-
Tooth discoloration	✔	-	-	-	-	-	-
Vomiting	✔	1-10	✔	<1	1-10	-	✔
Genitourinary							
Crystalluria	✔	-	-	-	-	-	-
Dysuria	-	-	-	<1	-	-	-
Hematuria	-	-	-	-	-	-	✔
Interstitial nephritis	-	-	✔	<1	<1	✔	✔
Renal tubular damage	-	-	-	-	-	✔	-
Urinary retention	-	-	-	<1	-	-	-
Vaginal mycosis	-	✔	-	-	-	-	-
Vaginitis	-	1-10	-	-	<1	-	-
Hematologic							
Agranulocytosis	✔	-	✔	-	<1	✔	✔
Anemia	✔	-	✔	-	-	-	-
Bone marrow depression	-	-	-	-	-	✔	-
Eosinophilia	✔	-	✔	-	<1	-	✔
Hemolytic anemia	✔	-	✔	-	<1	-	-
Leukopenia	✔	-	✔	-	<1	-	✔
Neutropenia	-	-	-	-	<1	✔	✔
Prothrombin time increased	-	✔	-	-	-	-	-
Thrombocytopenia	✔	-	-	<1	<1	-	✔
Thrombocytopenia purpura	✔	-	✔	-	-	-	-

Adverse Events	Amoxicillin	Amoxicillin/ Clavulanate	Ampicillin	Ampicillin/ Sulbactam	Dicloxacillin	Nafcillin	Oxacillin
Thrombocytosis	-	✔	-	-	-	-	-
Hepatic							
Acute cytolytic hepatitis	✔	-	-	-	-	-	-
Cholestatic jaundice	✔	✔	-	-	-	-	-
Hepatic cholestasis	✔	-	-	-	-	-	-
Hepatic dysfunction	-	✔	-	-	-	-	-
Hepatitis	-	✔	-	-	-	-	-
Hepatotoxicity	-	-	-	-	<1	-	✔
Laboratory Test Abnormalities							
Alkaline phosphatase increased	-	✔	-	-	-	-	-
Liver function tests increased	✔	✔	✔	<1	-	-	✔
Other							
Anaphylaxis	✔	-	✔	-	-	✔	-
Candidiasis	-	-	-	<1	-	-	-
Edema	-	-	-	<1	-	-	-
Epistaxis	-	-	-	<1	-	-	-
Hypersensitivity reaction	-	-	-	1-10	<1	✔	-
Hypersensitivity vasculitis	✔	-	-	-	-	-	-
Injection site reaction	-	-	-	-	-	✔	-
Laryngeal stridor	-	-	✔	-	-	-	-
Malaise	-	-	-	<1	-	-	-
Moniliasis	-	1-10	-	-	-	-	-
Pain at injection site	-	-	-	>10	-	✔	-
Serum sickness-like reaction	✔	-	✔	-	<1	✔	✔
Substernal pain	-	-	-	<1	-	-	-
Thrombophlebitis	-	-	-	1-10	-	✔	-
Vasculitis	-	✔	-	-	-	-	-

✔ Percent not specified
- Event not reported

Table 10. Adverse Drug Events (%) Reported with the Penicillins (Drugs P-T)[1-12]

Adverse Events	Penicillin G	Penicillin G Benzathine/ Penicillin G Procaine	Penicillin V	Piperacillin/ Tazobactam	Ticarcillin/ Clavulanate
Cardiovascular					
Arrhythmia	-	-	-	≤1	-
Atrial fibrillation	-	-	-	≤1	-
Bradycardia	-	-	-	≤1	-

Adverse Events	Penicillin G	Penicillin G Benzathine/ Penicillin G Procaine	Penicillin V	Piperacillin/ Tazobactam	Ticarcillin/ Clavulanate
Cardiac arrest	-	✔	-	≤1	-
Cardiac failure	-	-	-	≤1	-
Chest pain	-	-	-	≤1	-
Circulatory failure	-	-	-	≤1	-
Conduction disturbances	-	✔	-	-	-
Cyanosis	-	✔	-	-	-
Edema	-	-	-	≤1	-
Hypertension	-	-	-	2	-
Hypotension	-	✔	-	≤1	-
Myocardial depression	-	✔	-	-	-
Myocardial infarction	-	-	-	≤1	-
Pallor	-	✔	-	-	-
Palpitations	-	✔	-	-	-
Syncope	-	✔	-	≤1	-
Tachycardia	-	✔	-	≤1	-
Vasodilation	-	✔	-	-	-
Vasospasm	-	✔	-	-	-
Vasovagal reaction	-	✔	-	-	-
Ventricular fibrillation	-	-	-	≤1	-
Central Nervous System					
Agitation	-	-	-	2	-
Anxiety	-	✔	-	≤1	-
Cerebral vascular accident	-	✔	-	-	-
CNS stimulation	-	✔	-	-	-
Coma	✔	✔	-	-	-
Confusion	-	✔	-	≤1	✔
Depression	-	-	-	≤1	-
Dizziness	-	✔	-	≤1	-
Drowsiness	-	✔	-	-	✔
Euphoria	-	✔	-	-	-
Fatigue	-	✔	-	-	-
Fever	-	-	-	2-5	✔
Hallucination	-	-	-	≤1	-
Headache	-	✔	-	8	✔
Hyperreflexia	✔	-	-	-	-
Insomnia	-	-	-	7	-
Jarisch-Herxheimer reaction	✔	✔	-	-	✔

Adverse Events	Penicillin G	Penicillin G Benzathine/ Penicillin G Procaine	Penicillin V	Piperacillin/ Tazobactam	Ticarcillin/ Clavulanate
Myoclonus	✔	-	-	-	-
Nervousness	-	✔	-	-	-
Numbness	-	✔	-	-	-
Seizures	✔	✔	<1	≤1	✔
Somnolence	-	✔	-	-	-
Tremor	-	✔	-	≤1	-
Vertigo	-	-	-	≤1	-
Dermatologic					
Abscess	-	✔	-	2	-
Atrophy	-	✔	-	-	-
Bruising	-	✔	-	-	-
Cellulitis	-	✔	-	-	-
Contact dermatitis	✔	-	-	-	-
Diaphoresis	-	-	-	≤1	-
Edema	-	✔	-	-	-
Erythema multiforme	-	-	-	≤1	✔
Flushing	-	-	-	≤1	-
Gangrene	-	✔	-	-	-
Hemorrhage	-	✔	-	-	-
Inflammation	-	✔	-	≤1	-
Lump	-	✔	-	-	-
Necrosis	-	✔	-	-	-
Pain	-	✔	-	2	-
Photophobia	-	-	-	≤1	-
Pruritus	-	-	-	3	✔
Purpura	-	-	-	≤1	-
Rash	✔	-	-	4	✔
Skin ulcer	-	✔	-	-	-
Stevens-Johnson syndrome	-	-	-	≤1	✔
Toxic epidermal necrolysis	-	-	-	≤1	✔
Urticaria	-	-	-	-	✔
Gastrointestinal					
Abdominal pain	-	-	-	1-2	-
Bloody stool	-	✔	-	-	-
C. difficile colitis	-	-	-	-	✔
Constipation	-	-	-	1-8	-
Diarrhea	-	-	>10	7-11	✔

Adverse Events	Penicillin G	Penicillin G Benzathine/ Penicillin G Procaine	Penicillin V	Piperacillin/ Tazobactam	Ticarcillin/ Clavulanate
Flatulence	-	-	-	≤1	-
Gastritis	-	-	-	≤1	-
Ileus	-	-	-	≤1	-
Intestinal necrosis	-	✔	-	-	-
Nausea	-	-	>10	7	✔
Oral candidiasis	-	-	>10	-	-
Pseudomembranous colitis	✔	-	-	≤1	-
Stool changes	-	-	-	2	-
Taste perversion	-	-	-	≤1	-
Thirst	-	-	-	≤1	-
Ulcerative stomatitis	-	-	-	≤1	-
Vomiting	-	-	>10	3-4	✔
Genitourinary					
Dysuria	-	-	-	≤1	-
Genital pruritus	-	-	-	≤1	-
Hematuria	-	✔	-	≤1	-
Impotence	-	✔	-	-	-
Incontinence	-	-	-	≤1	-
Interstitial nephritis	✔	✔	<1	≤1	✔
Leukorrhea	-	-	-	≤1	-
Myoglobinuria	-	✔	-	-	-
Neurogenic bladder	-	✔	-	-	-
Oliguria	-	-	-	≤1	-
Priapism	-	✔	-	-	-
Proteinuria	-	✔	-	-	-
Renal failure	-	✔	-	≤1	-
Renal tubular damage	✔	-	-	-	-
Urinary retention	-	-	-	≤1	-
Vaginitis	-	-	-	≤1	-
Hematologic					
Agranulocytosis	-	-	-	≤1	-
Anemia	-	-	-	≤1	-
Bleeding	-	-	-	-	✔
Eosinophilia	-	-	-	-	✔
Hemolytic anemia	✔	✔	<1	≤1	✔
Leukopenia	-	-	-	-	✔
Neutropenia	✔	✔	-	-	✔

Adverse Events	Penicillin G	Penicillin G Benzathine/ Penicillin G Procaine	Penicillin V	Piperacillin/ Tazobactam	Ticarcillin/ Clavulanate
Pancytopenia	-	-	-	≤1	-
Positive Coombs' reaction	✔	✔	<1	-	✔
Prothrombin time prolonged	-	-	-	-	✔
Thrombocytopenia	-	-	-	≤1	✔
Thrombocytosis	-	-	-	≤1	-
Hepatic					
Hepatitis	-	-	-	≤1	-
Hepatotoxicity	-	-	-	-	✔
Jaundice	-	-	-	≤1	✔
Liver function tests increased	-	✔	-	1-10	-
Laboratory Test Abnormalities					
BUN increased	-	✔	-	-	-
Electrolyte imbalance	✔	-	-	-	✔
Hypoglycemia	-	-	-	≤1	-
Serum creatinine increased	-	✔	-	-	✔
Musculoskeletal					
Arthralgia	-	-	-	≤1	-
Arthritis exacerbation	-	✔	-	-	-
Back pain	-	-	-	≤1	-
Joint disorder	-	✔	-	-	-
Myalgia	-	-	-	≤1	-
Periostitis	-	✔	-	-	-
Rhabdomyolysis	-	✔	-	-	-
Traverse myelitis	-	✔	-	-	-
Weakness	-	✔	-	-	-
Respiratory					
Bronchospasm	-	-	-	≤1	-
Coughing	-	-	-	≤1	-
Dyspnea	-	-	-	3	-
Pharyngitis	-	-	-	2	-
Other					
Anaphylaxis	✔	-	-	≤1	✔
Blindness	-	✔	-	-	-
Blurred vision	-	✔	-	-	-
Candidiasis	-	-	-	≤1	-
Diaphoresis	-	✔	-	-	-
Epistaxis	-	-	-	≤1	-

Adverse Events	Penicillin G	Penicillin G Benzathine/ Penicillin G Procaine	Penicillin V	Piperacillin/ Tazobactam	Ticarcillin/ Clavulanate
Hemorrhage	-	-	-	≤1	-
Hiccough	-	-	-	≤1	-
Hypersensitivity reaction	✔	✔	-	-	✔
Infection	-	-	-	2	-
Injection site reaction	✔	-	-	≤1	-
Lymphadenopathy	-	✔	-	-	-
Malaise	-	-	-	≤1	-
Mesenteric embolism	-	-	-	≤1	-
Moniliasis	-	-	-	2	-
Mottling	-	✔	-	-	-
Myoclonus	-	✔	-	-	✔
Neurovascular damage	-	✔	-	-	-
Pseudoanaphylactic reaction	-	✔	-	-	-
Pulmonary edema	-	-	-	≤1	-
Pulmonary embolism	-	-	-	≤1	-
Rhinitis	-	-	-	≤1	-
Rigors	-	-	-	≤1	-
Sepsis	-	-	-	2	-
Serum sickness-like reaction	✔	✔	-	-	-
Thrombophlebitis	✔	✔	-	≤1	✔
Tinnitus	-	-	-	≤1	-
Warmth	-	✔	-	-	-

✔ Percent not specified
\- Event not reported

Table 11. Boxed Warning for the Penicillin G Benzathine and Penicillin G Benzathine/Penicillin G Procaine [1]

WARNING
Not for intravenous use. Do not inject intravenously or admix with other intravenous solutions. There have been reports of inadvertent intravenous administration of penicillin G benzathine which has been associated with cardiorespiratory arrest and death. Prior to administration of this drug, carefully read the warnings, adverse reactions, and dosage and administration sections of the labeling.

VII. Dosing and Administration

The usual dosing regimens for the penicillins are listed in Table 12.

Table 12. Usual Dosing Regimens for the Penicillins[1-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amoxicillin	Ear, Nose, and Throat Infections: Mild/moderate: 500 mg every 12 hours or 250 mg every 8 hours Severe: 875 mg every 12 hours or 500 mg every 8 hours Genitourinary Tract Infections: Mild/moderate: 500 mg every 12 hours or 250 mg every 8 hours Severe: 875 mg every 12 hours or 500 mg every 8 hours Gonorrhea (Acute), Anogenital Infections (Uncomplicated), Urethral Infections: 3 g as a single dose *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence: Dual therapy: 1 gram amoxicillin and 30 mg lansoprazole given three times daily for 14 days Triple therapy: 1 gram amoxicillin, 500 mg clarithromycin, and 30 mg lansoprazole given twice daily for 14 days Lower Respiratory Tract Infections: Mild/moderate or severe: 875 mg every 12 hours or 500 mg every 8 hours	Ear, Nose, and Throat Infections: >3 months of age: Mild/moderate: 25 mg/kg/day in divided doses every 12 hours or 20 mg/kg/day in divided doses every 8 hours Severe: 45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every 8 hours Genitourinary Tract Infections: >3 months of age: Mild/moderate: 25 mg/kg/day in divided doses every 12 hours or 20 mg/kg/day in divided doses every 8 hours Severe: 45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every 8 hours Gonorrhea (Acute), Anogenital Infections (Uncomplicated), Urethral Infections: Prepubertal children (≥2 years of age): 50 mg/kg amoxicillin, combined with 25 mg/kg probenecid as a single dose Lower Respiratory Tract Infections: >3 months of age: Mild/moderate or severe: 45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses	Capsule: 250 mg 500 mg Chewable tablet: 125 mg 250 mg Suspension: 125 mg/5 ml 200 mg/5 ml 250 mg/5 ml 400 mg/5 ml Tablet: 500 mg 875 mg Tablet (ER): 775 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Skin and Skin-Structure Infections: Mild/moderate: 500 mg every 12 hours or 250 mg every 8 hours Severe: 875 mg every 12 hours or 500 mg every 8 hours Tonsillitis and/or Pharyngitis: Tablet (ER): 775 mg once daily for 10 days with a meal	every 8 hours Skin and Skin-Structure Infections: >3 months of age: Mild/moderate: 25 mg/kg/day in divided doses every 12 hours or 20 mg/kg/day in divided doses every 8 hours Severe: 45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every 8 hours Tonsillitis and/or Pharyngitis: ≥12 years of age: Tablet (ER): 775 mg once daily for 10 days with a meal Unspecified Infections: ≤3 months of age: 30 mg/kg/day divided every 12 hours	
Amoxicillin and clavulanate	Acute Bacterial Sinusitis: Tablet (ER): Two tablets every 12 hours for 10 days Pneumonia (Community-Acquired): Tablet (ER): Two tablets every 12 hours for 7 to 10 days Unspecified Infections: Chewable tablet, suspension, tablet (IR): 500 mg every 12 hours or 250 mg every 8 hours	Acute Bacterial Sinusitis: ≥40 kg: Tablet (ER): Two tablets every 12 hours for 10 days Less Severe Infections: >3 months of age: Chewable tablets/suspension: 25 mg/kg/day divided every 12 hours or 20 mg/kg/day divided every 8 hours Otitis Media, Sinusitis, Lower Respiratory Tract Infections, More Severe Infections: >3 months of age: Chewable tablets/suspension: 45 mg/kg/day divided every 12 hours or 40 mg/kg/day divided every 8 hours Pneumonia (Community-Acquired): ≥40 kg: Tablet (ER): Two tablets every 12 hours for 7 to 10 days Severe Infections and Infections of the Respiratory Tract: ≥40 kg: Chewable tablet, suspension,	Chewable tablet: 200-28.5 mg 400-57 mg Suspension: 200-28.5 mg/5 ml 250-62.5 mg/5 ml 400-57 mg/5 ml 600-42.9 mg/5 ml Tablet: 250-125 mg 500-125 mg 875-125 mg Tablet (ER): 1,000-62.5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		tablet (IR): 875 mg every 12 hours or 500 mg every 8 hours Unspecified Infections: ≤3 months of age: 30 mg/kg/day divided every 12 hours >3 months of age: 200 to 400 mg every 12 hours or 125 to 250 mg every 8 hours ≥40 kg: Chewable tablet, suspension, tablet (IR): 500 mg every 12 hours or 250 mg every 8 hours	
Ampicillin	Gastrointestinal and Genitourinary Tract Infections: Injection (IM/IV): 500 mg every 6 hours Oral: 500 mg 4 times daily Gonorrhea (Men and Women): Oral: 3.5 grams as a single dose administered simultaneously with 1 g of probenecid Meningitis: Injection: 150 to 200 mg/kg/day. Start with IV administration for at least 3 days and continue with the IM route every 3 to 4 hours. Respiratory Tract Infections: Injection (IM/IV): 250 to 500 mg every 6 hours Septicemia: Injection: 150 to 200 mg/kg/day. Start with IV administration for at least 3 days and continue with the IM route every 3 to 4 hours. Soft Tissue Infections: Injection (IM/IV): 250 to 500 mg every 6 hours Urethritis (Males): Injection (IM/IV): 2 doses of 500 mg each at an interval of 8 to 12 hours	Gastrointestinal and Genitourinary Tract Infections: Injection (IM/IV): <40 kg: 50 mg/kg/day in divided doses at 6- to 8- hour intervals ≥40 kg: 500 mg every 6 hours Oral: ≤20 kg: 100 mg/kg/day in divided doses administered 4 times daily >20 kg: 500 mg 4 times daily Meningitis: Injection: 150 to 200 mg/kg/day. Start with IV administration for at least 3 days and continue with the IM route every 3 to 4 hours. Respiratory Tract Infections: Injection (IM/IV): <40 kg: 25 to 50 mg/kg/day in divided doses at 6- to 8- hour intervals ≥40 kg: 250 to 500 mg every 6 hours Septicemia: Injection: 150 to 200 mg/kg/day. Start with IV administration for at least 3 days and continue with the IM route every 3 to 4 hours. Soft Tissue Infections: Injection (IM/IV): <40 kg: 25 to 50 mg/kg/day in	Capsule: 250 mg 500 mg Injection: 125 mg 250 mg 500 mg 1 g 2 g 10 g Suspension: 125 mg/5 ml 250 mg/5 ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		divided doses at 6- to 8- hour intervals ≥40 kg: 250 to 500 mg every 6 hours Oral: ≤20 kg: 50 mg/kg/day in divided doses administered 3 to 4 times daily >20 kg: 250 mg 4 times daily	
Ampicillin and sulbactam	Unspecified Infections: 1.5 to 3 g IM/IV every 6 hours	Unspecified Infections: ≥1 year of age: ≤40 kg: 300 mg/kg IV every 6 hours >40 kg: 1.5 to 3 g IM/IV every 6 hours	Injection: 1.5 g 3 g 15 g
Dicloxacillin	Unspecified Infections: 125 to 250 mg every 6 hours	Unspecified Infections: <40 kg: 12.5 to 25 mg/kg/day divided every 6 hours ≥40 kg: 125 to 250 mg every 6 hours	Capsule: 250 mg 500 mg
Nafcillin	Unspecified Infections: Mild/moderate: 500 mg IM every 4 to 6 hours or 500 mg IV every 4 hours Severe: 1 g IM/IV every 4 hours	Unspecified Infections: Neonates: 10 mg/kg IM twice daily <40 kg: 25 mg/kg IM twice daily ≥40 kg: 500 mg IM every 4 to 6 hours or 500 mg IV every 4 hours	Injection: 1 g 1 g/50 ml 2 g 2 g/100 ml 10 g
Oxacillin	Mild to Moderate Infections: 250 to 500 mg IM/IV every 4 to 6 hours Severe Infections: 1 g IM/IV every 4 to 6 hours	Mild to Moderate Infections: <40 kg: 50 mg/kg/day IM/IV in divided doses every 6 hours ≥40 kg: 250 to 500 mg IM/IV every 4 to 6 hours Severe Infections: <40 kg: 100 mg/kg/day IM/IV in divided doses every 4 to 6 hours ≥40 kg: 1 g IM/IV every 4 to 6 hours Unspecified Infections: Premature and neonates: 25 mg/kg/day IM/IV	Injection: 1 g 2 g 10 g
Penicillin G benzathine	Prophylaxis (Rheumatic Fever and Glomerulonephritis): 1,200,000 units IM once a month or 600,000 units IM every 2 weeks Streptococcal (Group A) Upper Respiratory Tract Infections: 1,200,00 units IM as a single dose	Streptococcal (Group A) Upper Respiratory Tract Infections: <60 pounds: 300,000-600,000 units IM as a single dose Older pediatric patients: 900,000 units IM as a single dose Syphilis (Congenital): <2 years of age: 50,000	Injection: 600,000 units/ml 1.2 MMU/2 ml 2.4 MMU/4 ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Syphilis: Primary, secondary and latent: 2,400,000 units IM as a single dose Late and neurosyphilis: 2,400,000 units IM at 7-day intervals for 3 doses Yaws, Bejel, Pinta: 1,200,000 units IM as a single dose	units/kg IM as a single dose 2 to 12 years of age: Adjust dosage based on adult dosage schedule	
Penicillin G benzathine and penicillin G procaine	Erysipelas: 2,400,000 units IM as a single dose Pneumococcal Infections (Except Pneumococcal Meningitis): 1,200,000 units IM repeated every 2 to 3 days until the temperature is normal for 48 hours Scarlet Fever: 2,400,000 units IM as a single dose Skin and Soft-Tissue Infections: 2,400,000 units IM as a single dose Upper Respiratory Tract Infections: 2,400,000 units IM as a single dose	Erysipelas: <30 pounds: 600,000 units IM as a single dose 30-60 pounds: 900,000 to 1,200,000 units IM as a single dose >60 pounds: 2,400,000 units IM as a single dose Pneumococcal Infections (Except Pneumococcal Meningitis): 600,000 units IM repeated every 2 to 3 days until the temperature is normal for 48 hours Scarlet Fever: <30 pounds: 600,000 units IM as a single dose 30-60 pounds: 900,000 to 1,200,000 units IM as a single dose >60 pounds: 2,400,000 units IM as a single dose Skin and Soft-Tissue Infections: <30 pounds: 600,000 units IM as a single dose 30-60 pounds: 900,000 to 1,200,000 units IM as a single dose >60 pounds: 2,400,000 units IM as a single dose Upper Respiratory Tract Infections: <30 pounds: 600,000 units IM as a single dose 30-60 pounds: 900,000 to 1,200,000 units IM as a single dose >60 pounds: 2,400,000 units	Injection: 900-300 units/2 ml 1.2 MMU/2 ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		IM as a single dose	
Penicillin G (potassium and sodium)	Actinomycosis: Cervicofacial:1 to 6 million units/day Thoracic and abdominal disease: 10 to 20 million units/day Anthrax: A minimum 5 to 8 million units/day until cure is effected Clostridial Infections: 20 million units/day as an adjunct to antitoxin Diphtheria: 2 to 3 million units/day in divided doses for 10 to 12 days Erysipeloid Endocarditis: 12 to 20 million units/day for 4 to 6 weeks Fusospirochetal Infections (Severe Infections of Oropharynx, Lower Respiratory Tract and Genital Area): 5 to 10 million units/day Gonococcal Infections (Disseminated): Arthritis, meningitis, endocarditis: 10 million units/day Gram-Negative Bacillary Infections (Bacteremia): 20 to 80 million units/day Haverhill Fever: 12 to 20 million units/day for 3 to 4 weeks Listeria Infections: Endocarditis: 15 to 20 million units/day for 4 weeks Meningitis: 15 to 20 million units/day for 2 weeks Meningococcal Meningitis: 1 to 2 million units IM every 2 hours or 24 million units/day	Diphtheria: 150,000 to 250,000 units/kg/day in divided doses every 6 hours for 7 to 10 days Gonococcal Infections (Disseminated): <45 kg: Arthritis: 100,000 units/kg/day in 4 equally divided doses for 7 to 10 days Meningitis: 250,000 units/kg/day in equal doses every 4 hours for 10 to 14 days Endocarditis: 250,000 units/kg/day in equal doses every 4 hours for 4 weeks ≥45 kg: Arthritis, meningitis, endocarditis: 10 million units/day in 4 equally divided doses Haverhill Fever: 150,000 to 250,000 units/kg/day in equal doses every 4 hours for 4 weeks Listeria Infections: Neonates: 500,000 to 1 million units/day Meningitis (Pneumococcus and Meningococcus): 250,000 units/kg/day divided in equal doses every 4 hours for 7 to 14 days Rat-Bite Fever: 150,000 to 250,000 units/kg/day in equal doses every 4 hours for 4 weeks Serious Infections (Streptococci and Meningococcus): 150,000 to 300,000 units/kg/day divided in equal doses every 4 to 6 hours Syphilis (Congenital and Neurosyphilis):	Injection (Potassium): 1 MMU/50 ml 2 MMU/50 ml 3 MMU/50 ml 5 million units 20 million units Injection (Sodium): 5 million units

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	IV as 2 million units every 2 hours Pasteurella Infections (Bacteremia and Meningitis): 4 to 6 million units/day for 2 weeks Rat-Bite Fever: 12 to 20 million units/day for 3 to 4 weeks Septicemia: 1 to 2 million units IM every 2 hours or 24 million units/day IV as 2 million units every 2 hours Serious Infections (Streptococci, Pneumococci, and Staphylococci): 5 to 24 million units in divided doses every 4 to 6 hours Syphilis and Neurosyphilis: 2 to 4 million units every 4 hours for 10 to 14 days	50,000 units/kg every 4 to 6 hours for 10 to 14 days	
Penicillin G procaine	Anthrax: Cutaneous: 600,000 to 1 million units/day IM Inhalational (postexposure): 1.2 million units IM every 12 hours Bacterial Endocarditis: 600,000 to 1 million units/day IM Diphtheria: Adjunctive therapy with antitoxin: 300,000 to 600,000 units/day IM Carrier state: 300,000 units/day IM for 10 days Erysipelas: 600,000 to 1 million units/day IM for at least 10 days Fusospirochetosis (Vincent's Infection): 600,000 to 1 million units/day IM	Anthrax: (Inhalational Postexposure): 25,000 units/kg every 12 hours Pneumonia: <60 pounds: 300,000 units/day IM Staphylococcal Infections: <60 pounds: 300,000 units/day IM Streptococcal Infections: <60 pounds: 300,000 units/day IM Syphilis: >12 years of age: Primary, secondary and latent: 600,000 units/day IM for 8 days Late: 600,000 units/day IM for 10 to 15 days <70 pounds: Congenital: 50,000 units/kg/day for 10 days	Injection: 600,000 units 1.2 MMU

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Pneumonia (Moderately Severe and Uncomplicated): 600,000 to 1 million units/day IM Rat-Bite Fever: 600,000 to 1 million units/day IM Scarlet Fever: 600,000 to 1 million units/day IM for at least 10 days Skin and Soft-Tissue Infections: 600,000 to 1 million units/day IM for at least 10 days Staphylococcal Infections (Moderately Severe to Severe): 600,000 to 1 million units/day IM Streptococcal Infections: 600,000 to 1 million units/day IM for at least 10 days Syphilis: Primary, secondary and latent: 600,000 units/day IM for 8 days Late: 600,000 units/day IM for 10 to 15 days Tonsillitis (Moderately Severe to Severe): 600,000 to 1 million units/day IM for at least 10 days Upper Respiratory Tract Infections: 600,000 to 1 million units/day IM for at least 10 days Yaws, Bejel, Pinta: Treatment as for syphilis in corresponding stage of disease		
Penicillin V potassium	Chorea (Prophylaxis): 125 to 250 mg twice daily on a continuing basis Erysipelas: 125 to 250 mg every 6 to 8 hours for 10 days	Chorea (Prophylaxis): ≥12 years of age: 125 to 250 mg twice daily on a continuing basis Erysipelas: ≥12 years of age: 125 to 250 mg every 6 to 8	Suspension: 125 mg/5 ml 250 mg/5 ml Tablet: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Fusospirochetosis (Vincent's Infection) of the Oropharynx: 250 to 500 mg every 6 to 8 hours Pneumococcal Infections: 250 to 500 mg every 6 hours Prophylaxis (Procedures): 2 g one hour before procedure and 1 g 6 hours later Otitis Media: 250 to 500 mg every 6 hours Rheumatic Fever (Prophylaxis): 125 to 250 mg twice daily on a continuing basis Scarlet Fever: 125 to 250 mg every 6 to 8 hours for 10 days Skin and Soft-Tissue Infections: 250 to 500 mg every 6 to 8 hours Staphylococcal Infections: 250 to 500 mg every 6 to 8 hours Streptococcal Infections: 125 to 250 mg every 6 to 8 hours for 10 days	hours for 10 days Fusospirochetosis (Vincent's Infection) of the Oropharynx: ≥12 years of age: 250 to 500 mg every 6 to 8 hours Pneumococcal Infections: ≥12 years of age: 250 to 500 mg every 6 hours Prophylaxis (Procedures): <60 pounds: 1 g one hour before procedure and 1 g 6 hours later ≥12 years of age: 2 g one hour before procedure and 1 g 6 hours later Otitis Media: ≥12 years of age: 250 to 500 mg every 6 hours Rheumatic Fever (Prophylaxis): ≥12 years of age: 125 to 250 mg twice daily on a continuing basis Scarlet Fever: ≥12 years of age: 125 to 250 mg every 6 to 8 hours for 10 days Skin and Soft-Tissue Infections: ≥12 years of age: 250 to 500 mg every 6 to 8 hours Staphylococcal Infections: ≥12 years of age: 250 to 500 mg every 6 to 8 hours Streptococcal Infections: ≥12 years of age: 125 to 250 mg every 6 to 8 hours for 10 days	
Piperacillin and tazobactam	Pneumonia (Nosocomial): 4.5 g IV every 6 hours with an aminoglycoside for 7 to 14 days	Appendicitis and Peritonitis: 2-9 months of age: 80 mg piperacillin/10 mg tazobactam per kg IV every 8 hours for 7 to 10 days	Injection: 2.25 g 2.25 g/50 ml 3.375 g 3.375 g/50 ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Unspecified Infections: 3.375 g IV every 6 hours for 7 to 10 days	≥9 months of age (up to 40 kg): 100 mg piperacillin/12.5 mg tazobactam per kg IV every 8 hours for 7 to 10 days >40 kg: 3.375 g every 6 hours for 7 to 10 days	4.5 g 4.5 g/100 ml 40.5 g
Ticarcillin and clavulanate	Gynecologic Infections: Moderate: 200 mg/kg/day divided every 6 hours Severe: 300 mg/kg/day divided every 4 hours Unspecified Infections: 3.1 g IV every 4 to 6 hours	Unspecified Infections: ≥3 months of age: <60 kg: Mild to moderate: 200 mg/kg/day in divided doses every 6 hours Severe: 300 mg/kg/day in divided doses every 4 hours ≥60 kg: Mild to moderate: 3.1 g every 6 hours Severe infections: 3.1 g every 4 hours	Injection: 3.1 g 3.1 g/0.1 L 31 g

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the penicillins are summarized in Table 13.

Table 13. Comparative Clinical Trials with the Penicillins

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Dermatological Infections				
Dagan et al.[68] (1989) Amoxicillin 40 mg/kg/day in three divided doses for 10 days vs amoxicillin-clavulanate 40 mg/kg/day for 10 days	DB, PRO Children 6 months to 9 years of age with culture-positive (*S aureus* or β-hemolytic *Streptococcus*) nonbullous impetigo	N=51 10 days	Primary: Impetigo markedly improved or cured Secondary: New lesions	Primary: Amoxicillin-clavulanate resulted in faster clinical improvement compared to amoxicillin (95% vs 68% at 5 days, P<0.05) and showed a trend toward more clinical improvement at 10 days (96% vs 80%, P=NS). Secondary: Amoxicillin-clavulanate resulted in fewer new lesions at 10 days (0% vs 20%, P<0.05).
Vick Fragoso et al.[32] (2009) Amoxicillin-clavulanate 1,000 mg-200 mg IV three times daily for at least 3 days followed by 500 mg-125 mg orally three times daily for 7 to 21 days vs	RCT, OL, MC Patients ≥18 years of age with complicated skin and skin-structure infections (cSSSI)	N=804 21 days	Primary: Clinical response at TOC for the PP population Secondary: Clinical response at TOC for the ITT population and clinical response at TOC by indication, bacteriological success at TOC for the PP/MBE population	Primary: Clinical cure (success) rates at TOC for the PP population were not significantly different between the treatment groups: 80.6% for moxifloxacin compared with 84.5% for amoxicillin/clavulanate. These efficacy findings were supported by results for the ITT population: 72.7% for moxifloxacin compared with 74.8% for amoxicillin/clavulanate. Moxifloxacin was not inferior to amoxicillin/clavulanate for cSSSIs. Clinical success rates by indication were not significantly different among the treatment groups. The highest clinical success rates were for complicated erysipelas, abscess and surgical wound infection, and the lowest clinical success rates were for necrotizing fasciitis and diabetic foot infection. Clinical response rates in patients with a diabetic foot infection were similar between the two groups in patients with the most severe infections. Among the PP population, 19.4% of moxifloxacin- treated and 15.5% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
moxifloxacin 400 mg IV once daily for at least 3 days followed by 400 mg orally for 7 to 21 days The decision to switch from IV to oral therapy was based on clinical response.				amoxicillin/clavulanate-treated patients were clinical failures at TOC. There were no significant differences in bacteriological success rates at TOC in the PP/MBE population between moxifloxacin-treated patients (76.0%) and amoxicillin/clavulanate-treated patients (81.4%; 95% CI, -12.96 to 4.41; P=0.59).
Azimi et al.[93] (1999) Ampicillin-sulbactam 150-300 mg/kg/day divided every 6 hours vs cefuroxime 50-100 mg/kg/day divided every 6 or 8 hours	RCT, OL, MC Pediatric patients 3-11 years of age with serious skin and skin structure infections	N=98 14 days	Primary: Clinical response, bacteriologic response	Primary: Cure rate was 78% in the ampicillin-sulbactam group vs 76.9% in the cefuroxime group (P=NS). Bacteriologic eradication rate was 93.2% in the ampicillin-sulbactam group vs 100% in the cefuroxime group (P=NS).
Stevens et al.[69] (2000) Oxacillin 2 g IV every 6 hours followed by dicloxacillin 500 mg orally every 6 hours vs	RCT, DB, MC Patients with complicated skin and soft tissue infections	N=819 Variable duration	Primary: Clinical response (cure rate)	Primary: Clinical cure rate was 64.9% in the oxacillin/dicloxacillin group vs 69.8% in the linezolid group (P=0.141).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
linezolid 600 mg IV every 12 hours				
Tong et al.[28] (2010) Penicillin benzathine 45 mg/kg IM as a single dose vs sulfamethoxazole-trimethoprim 20 + 4 mg/kg twice daily for 5 days	RCT Aboriginal children 2 months to 16 years of age with impetigo	N=13 7 days	Primary: Successful treatment of impetigo lesions at day 7 after the commencement of treatment Secondary: Bacterial resolution of sores at day 4 and day 7; successful treatment at day 4	Primary: Treatment was successful in all 7 patients assigned to sulfamethoxazole-trimethoprim, and 5 of 6 patients assigned to the penicillin group 7 days after randomization (P=0.46). Secondary: By day 4, microbiological clearance was documented in 5 of 7 patients treated with sulfamethoxazole-trimethoprim and in 2 of 6 patients treated with penicillin (P=0.28). By day 7, microbiological clearance was documented in all 7 patients treated with sulfamethoxazole-trimethoprim and in 3 of 6 patients treatment with penicillin (P=0.07). Treatment was successful after 4 days in 6 of 7 treated with sulfamethoxazole-trimethoprim and 3 of 6 with penicillin (P=0.27).
Harkless et al.[90] (2005) Piperacillin-tazobactam 4 g/0.5 g every 8 hours vs ampicillin-sulbactam 2 g/1 g every 6 hours	RCT, OL, MC Adult patients with moderate-to-severe infected diabetic foot ulcers	N=314 9-10 days	Primary: Clinical efficacy rates (cure or improvement) Secondary: Bacteriologic success rates, adverse events	Primary: Clinical success rates were similar for both treatment groups (71.2% for piperacillin-tazobactam vs 66.7% for ampicillin-sulbactam, P=NS). Secondary: Bacteriologic success rates were similar for both treatment groups (P=NS). Incidence and severity of adverse events were similar between the two treatment groups (P=NS).
Saltoglu et al.[26] (2010) Piperacillin-tazobactam 4.5 g IV every 8 hours for 14 to 28 days	RCT, OL, SC Patients ≥18 years of age with a diagnosis of moderate to severe diabetic lower	N=64 2 months post-treatment	Primary: Clinical response Secondary: Relapse rate after 2 months	Primary: A successful clinical response was seen in 46.7% of patients in the Pip-Tazo group and in 28.1% of patients in the IMP group (RR, 1.6; (95% CI, 0.84–3.25; P=0.130). Secondary: During 2 months follow-up, two patients in the IMP group and none in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(Pip-Tazo) vs imipenem-cilastatin 0.5 g IV every 6 hours for 14 to 28 days (IMP)	extremity foot infection			PIP-Tazo group relapsed (RR, 2; 95% CI, 0.94–4.24; P=0.058). Sixty-four percent of patients had amputations. There was no significant difference in amputation rates between the Pip-Tazo and IMP groups (60% vs 68.8%; P=0.739).
Tan et al.[91] (1993) Piperacillin-tazobactam 3 g/375 mg every 6 hours vs ticarcillin-clavulanate 3 g/100 mg every 6 hours	RCT, DB, MC Hospitalized patients with complicated skin and skin structure infections	N=251 10-14 days	Primary: Clinical outcome Secondary: Bacteriological outcome	Primary: No significant difference in the overall clinical response was observed. The percentages of cured/improved/favorable outcomes were similar (61%/15%/76% for the piperacillin-tazobactam group vs 61%/16%/77% for the ticarcillin-clavulanate group, P=1.00). Secondary: No statistically significant differences in microbial eradication rates were observed between treatment groups (P=NS for monomicrobial infections and polymicrobial infections).
Clay et al.[92] (2004) Ticarcillin-clavulanate 3.1 g every 6 hours (TC) vs metronidazole 1 g plus ceftriaxone QD (MTZ + CTX)	PRO, OL Hospitalized older male patients (mean age of 63.8 years) with diabetic lower-extremity infections	N=70 Duration not specified	Primary: Treatment success at 96 hours or at discontinuation of antibiotic	Primary: Treatment success was not significantly different between treatment groups at 96 hours (86% for MTZ + CTX group vs 82% for TC group, P=NS) and on final day of therapy (72% for MTZ + CTX group vs 76% for TC group, P=NS).
Genitourinary Infections				
Brathwaite et al.[70]	RCT, DB, PRO	N=160	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(1979) Amoxicillin 3 g as a single dose vs ampicillin 3 g as a single dose Both groups with probenecid 1 g pretreatment.	Men with uncomplicated gonorrhea	14 days	Cure rate (microbial and clinical resolution) Secondary: Adverse effects	Amoxicillin and ampicillin both had 98.6% cure rates (P=NS). Secondary: No adverse effects were reported.
Felman et al.[72] (1979) Amoxicillin 3 g for one dose vs ampicillin 3.5 g for one dose	RCT, PRO Adults with uncomplicated gonorrhea	N=115 1 week	Primary: Culture negativity 1 week post-treatment Secondary: Adverse effects	Primary: Amoxicillin and ampicillin were similarly curative (100% vs 96.2%, P=0.18). Secondary: Four patients on amoxicillin and 2 patients on ampicillin had mild adverse events.
Latif et al.[73] (1984) Amoxicillin 3 g and clavulanate 250 mg for one dose vs penicillin procaine 2.4 million units IM for one dose	Unblinded Men with uncomplicated gonococcal urethritis	N=121 14 days	Primary: Microbial cure (culture negative 2 weeks post-treatment) Secondary: Infections due to penicillinase-producing *Neisseria*, post gonococcal urethritis	Primary: Amoxicillin resulted in a higher cure rate than penicillin (90.6% vs 73.7%, P=0.01). Secondary: The numbers of infections due to penicillinase producing *Neisseria* (7.8% vs 15.8%, P=NS) and post gonococcal urethritis (7.8% vs 14%, P=NS) were not statistically different between the two groups.
Gallacher et al.[76]	RCT, DB	N=67	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(1986) Amoxicillin-clavulanate 250/125 mg orally for 5 days vs amoxicillin 250 mg orally for 5 days	Elderly inpatients with urinary tract infections	5 days	Bacteriologic cure at end of treatment Secondary: Bacteriologic cure after conversion to amoxicillin-clavulanate	Amoxicillin-clavulanate was more effective than amoxicillin at achieving a negative urine culture (87.5% vs 43%, P<0.001). Secondary: Of the patients who failed amoxicillin, 62.5% responded to amoxicillin-clavulanate.
Fernandez et al.[85] (1990) <u>Mild Cases:</u> Amoxicillin-clavulanate 500 mg orally every 8 hours vs ampicillin 500 mg orally plus metronidazole 500 mg orally every 8 hours <u>Severe Cases:</u> Amoxicillin-clavulanate 1.2 g IV every 8 hours vs ampicillin 2 g IV	RCT, PRO Women with mild or severe endometritis	N=99 8 days	Primary: Clinical cure rate, treatment duration Secondary: Adverse effects	Primary: Time to defervescence was the same in both treatment groups (3.5 days vs 2.7 days, P=NS). Time to resolution of clinical symptoms was longer in the amoxicillin-clavulanate group (2.3 days vs 1.7 days, P<0.05), but when urinary tract infections were excluded, the difference was non-significant (2.3 days vs 2.1 days). Secondary: A rash developed in one patient from each group, but did not prompt discontinuation of therapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
every 8 hours plus aminoglycoside 1.5 mg/kg IM every 12 hours				
Cirau-Vigneron et al.[86] (1989) Amoxicillin 1 g and clavulanate 200 mg IV until improvement, then amoxicillin-clavulanate 500/125 mg (4-6 tablets per day) vs amoxicillin or ampicillin 3-4 g plus gentamicin 160 mg or dibekacin 150 mg or tobramycin 150 mg plus metronidazole 1.5 g daily until improvement, then amoxicillin or ampicillin 2-3 g plus metronidazole 1-1.5 g daily	RCT, MC Inpatient women with pelvic inflammatory disease	N=152 1 month	Primary: Mean duration of treatment, clinical response at time of discharge Secondary: Clinical response at 1 month and tolerance	Primary: Mean duration of treatment was the same in both groups. No significant difference in clinical response at time of discharge between amoxicillin-clavulanate and the combination therapy (96% vs 90%, P=NS). Secondary: No difference in treatment response at 1 month was observed (95% vs 95%). Adverse effects were similar between the two groups (2 patients with mild phlebitis in each group, 1 patient with vaginal candidiasis in the amoxicillin-clavulanate group, 1 patient with urticaria and genitourinary-gastrointestinal candidiasis in combination group).
Karney et al.[71] (1974) Ampicillin 3.5 g	RCT, DB Adults with uncomplicated	N=108 2 weeks	Primary: Bacteriologic culture negative at 2 weeks	Primary: Ampicillin and amoxicillin had similar bacteriologic cure rates at 2 weeks posttreatment (98.3% vs 95.8%) in anogenital gonorrhea.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
orally with probenecid 1 g orally for one dose vs amoxicillin 3 g orally for one dose	gonorrhea		posttreatment	
Spinnato et al.[88] (2000) Ampicillin as a single dose vs cefotetan as a single dose vs ampicillin-sulbactam as a single dose	RCT, PRO, DB Women who were being treated for prevention of post-Caesarean endomyometritis after umbilical cord clamping	N=298 Duration not specified	Primary: Clinical response (endomyometritis)	Primary: Frequency of endomyometritis was 4% in the ampicillin-sulbactam group, 4.2% in the cefotetan group, and 5.9% in the ampicillin group.
Resnik et al.[87] (1994) Ampicillin-sulbactam 1.5 g every 6 hours vs ampicillin 1 g IV every 6 hours plus gentamicin 1.5 mg/kg IV loading	RCT, PRO Inpatient women with early postpartum endometritis	N=76 48 hours	Primary: Clinical resolution within 48 hours of treatment initiation Secondary: Cost of drug and administration, length of stay, tolerability	Primary: Fewer patients on ampicillin-sulbactam achieved clinical resolution at 48 hours compared to the standard triple-antibiotic therapy (79.4% vs 90.4%, P=NS). Secondary: Length of hospital stay was the same between treatment groups (6.8 days), and side effects (rash) were only present in one patient of each group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
then 1 mg/kg IV every 8 hours and adjusted based on levels plus clindamycin 900 mg IV every 8 hours (standard triple-antibiotic therapy)				
Hook et al.[75] (2002) Penicillin benzathine G 2.4 million units for one dose vs azithromycin 2 g as a single dose or 2 g every week for two weeks	RCT Patients 18-56 years of age with early syphilis	N=74 12 months	Primary: Therapeutic response	Primary: The overall response rate for patients in the benzathine penicillin G group was 86%. The overall response rate for patients in the single-dose azithromycin group was 94%, which was not significantly different from the penicillin group (P=0.75). The overall response rate for patients in the double-dose azithromycin group was 83% and was not significantly different from the penicillin group (P=0.95).
Hook et al.[15] (2010) Penicillin benzathine G 2.4 million units IM as a single dose vs azithromycin 2 g as a single dose	RCT, MC, OL Patients 18 to 55 years of age with early syphilis (primary, secondary, or early latent)	N=517 6 months	Primary: Serological cure of infection	Primary: In the ITT analysis at the 6-month follow-up visit, 77.6% of azithromycin patients and 78.5% of penicillin patients experienced serological cure (1-sided lower bound of the 95% CI of the difference, −7.2%). In the PP analysis at the 6-month follow-up visit, 77.5%) of azithromycin patients and 78.9%) of penicillin patients experienced serological cure (1-sided 95% CI lower bound was −7.9%). The efficacy of 2 grams azithromycin administered orally was non-inferior to the administration of benzathine penicillin G for the treatment of early syphilis in patients without HIV infection.
Bai et al.[114] (2008)	MA	N=476 (4 trials)	Primary: Cure rates	Primary: In the azithromycin group, serology cure occurred in 95% of patients. In

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Penicillin G benzathine vs azithromycin	Patients ≥18 years old with early syphilis	Variable duration		the penicillin G benzathine group, serology cure occurred in 84.0% of patients (OR=1.37; 95% CI, 1.05, 1.77; P=0.02). The pooled OR for primary syphilis with the administration of azithromycin as compared to penicillin G benzathine was 0.69 (95% CI, 0.09–1.61; P=0.38). There was no significant difference in the rate of adverse events between the treatment groups.
Landis et al.[74] (1981) Piperacillin 2 g IM for one dose vs penicillin G 4.8 million units IM for one dose, with pre-administration of probenecid 1 g orally	RCT, PRO Men with uncomplicated gonococcal urethritis	N=127 7-10 days posttreatment	Primary: Clinical cure, bacteriologic cure	Primary: A total of 100% of the patients in both groups were reported as clinically and bacteriologically cured.
Cohn et al.[99] (2000) Piperacillin-tazobactam 3.375 g every 6 hours IV (PIP-TAZO) vs ciprofloxacin 400 mg every 12 hours IV plus metronidazole 500	RCT, MC, DB Adult patients with complicated intraabdominal infections	N=459 14 days	Primary: Clinical response rate (improvement in signs and symptoms as evaluated by the physician) Secondary: Bacteriologic response (eradication, of organism)	Primary: Clinical response rate of infection (symptom improvement) was higher in the CIP + MET group (74% vs 63%, P=0.047). Secondary: Bacteriologic eradication rates at the end of therapy were similar between treatment groups (77% for CIP + MET vs 71% for PIP-TAZO; 95% CI, -5.1, 19.4).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg every 6 hours IV (CIP + MET), switched to oral CIP + MET when determined to be appropriate by investigator				
Polk et al.[100] (1993) Piperacillin-tazobactam 3 g-375 mg every 6 hours vs clindamycin 600 mg every 6 hours and gentamicin 2.5-5 mg/kg/day given every 8-12 hours	RCT, PRO, OL Hospitalized patients with infection after intraabdominal surgery	N=331 4-6 weeks posttreatment	Primary: Favorable clinical response, favorable bacteriological response Secondary: Significant adverse effects, death	Primary: Favorable clinical response was greater for piperacillin-tazobactam compared to clindamycin + gentamicin (88% vs 77%, P=0.13). Favorable bacteriological response was greater in the piperacillin-tazobactam group (86% vs 75%, P=0.07). Secondary: The mortality rate of the two groups was similar (3.2% for the piperacillin-tazobactam group vs 4.4% for the clindamycin + gentamicin group). The incidence of clinically significant adverse events was similar between the two groups.
File et al.[107] (1985) Ticarcillin 80-160 mg/kg/day plus clavulanate 0.1-0.2 g every 8 hours IV vs piperacillin 125-200 mg/kg/day every 6-8 hours	RCT Adult patients with serious urinary tract infections	N=47 Mean 9.3 days	Primary: Clinical symptomatic response, bacterial response Secondary: Adverse events	Primary: Satisfactory symptomatic response was observed with all patients in the study. Bacteriologic eradication was 41% with ticarcillin-clavulanate and 55% with piperacillin. Secondary: Minimal adverse effects in 2 of ticarcillin-clavulanate- treated patients (rash and diarrhea).
Respiratory Infections				

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Stenstrom et al.[58] (1991) Amoxicillin 20 mg/kg/day for 10 days vs amoxicillin-clavulanate 20 mg/kg/day for 7 days	RCT, DB, PRO Children 6 months to 10 years of age with recurrent acute otitis media or failure of penicillin	N=102 30 days posttreatment	Primary: Clinical and bacteriological response at the last visit Secondary: Adverse effects	Primary: There was no significant difference between the amoxicillin-clavulanate and amoxicillin groups in clinical improvement rate (86.7% vs 86.1%, P=NS). There was no significant difference between the elimination, persistence, or re-colonization rate between the two groups, except that amoxicillin-clavulanate eliminated β-lactamase producing *B catarrhalis* more frequently than amoxicillin (67% vs 31%, P=0.02). Secondary: The two drugs were equally well tolerated (24% vs 20% had adverse effects, 1 patient vs 3 patients discontinued therapy).
Chan et al.[60] (1988) Amoxicillin 30 mg/kg/day given in three divided doses for 10 days vs amoxicillin-clavulanate 30 mg/kg/day given in three divided doses for 10 days	RCT, DB, MC Children 7 months to 12 years of age with otitis media with effusion (secretory otitis media) without symptoms of acute otitis media	N=108 16 weeks after start of therapy for responders	Primary: Clinical response (no effusion) at day 10 and 4 weeks after start of therapy, recurrence of effusion up to 16 weeks post-therapy in responders at 4 weeks Secondary: Adverse effects	Primary: Amoxicillin-clavulanate showed a trend toward better resolution of the effusion at 10 days compared to amoxicillin (51.8% vs 32%, P=0.06), but not at 4 weeks (50% vs 51%). Amoxicillin-clavulanate showed a trend toward reduced recurrence of effusion during a 16-week follow-up (36.4% vs 63.2%), but the difference was not statistically significant (P=0.16). Secondary: The adverse effect rate was similar in both groups, and the adverse events were mainly gastrointestinal or dermatological.
Jibril et al.[77] (1989) Amoxicillin 250-500 mg TID vs amoxicillin 250-	RCT, PRO, OL Children with bacterial pneumonia	N=100 Median 7 days	Primary: Clinical improvement Secondary: Time to clinical improvement, adverse reactions	Primary: Amoxicillin-clavulanate was more effective at achieving clinical improvement than amoxicillin (93.8% vs 60.4%, P<0.001). Secondary: Amoxicillin-clavulanate improved the symptoms more quickly than amoxicillin (2.92 days vs 3.58 days). Mild rash or diarrhea was seen in 2 patients on amoxicillin-clavulanate.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
500 mg and clavulanate 62.5-125 mg TID				
Jensen et al.[81] (1988) Amoxicillin 50 mg/kg/day plus probenecid 250-750 mg/day for 14 days vs amoxicillin 50 mg/kg/day and clavulanate (4:1 ratio) plus probenecid 250-750 mg/day	SB Outpatient children and adults with COPD and ampicillin sensitive *H influenzae*	N=71 2 week posttreatment	Primary: Clinical and microbial efficacy Secondary: Adverse events	Primary: No difference in clinical efficacy in symptomatic patients was observed (57% for amoxicillin, 59% for amoxicillin-clavulanate, P=NS). No difference in microbial eradication 2 weeks posttreatment between groups was observed (57% for amoxicillin, 70% for amoxicillin-clavulanate, P=NS). Treatment with amoxicillin-clavulanate was significantly better (P<0.05) than amoxicillin if more than one strain of *H influenza* was present. Beta-lactamase producing *H influenza* was detected at two weeks posttreatment in 29% of the amoxicillin group and 23% of the amoxicillin-clavulanate (P=NS). Secondary: Both groups experienced similar rates of adverse events (3%).
Morris et al.[17] (2010) Amoxicillin 50 mg/kg/day in two divided doses for a minimum of 7 days vs azithromycin 30 mg/kg as a single dose	RCT, SB Aboriginal children 6 months to 6 years of age with acute otitis media	N=320 Up to 21 days	Primary: Clinical failure (defined as persistent ear pain, bulging tympanic membrane or middle ear discharge) at the end of therapy visit (days 6 to 11), failure to improve (defined as no improvement in clinical signs at the end of therapy at the end of therapy visit (days 6 to 11)	Primary: At the end of therapy, 50% of patients receiving azithromycin and 54% of patients receiving amoxicillin were clinical failures (P=0.504). At the end of therapy, 45% of patients receiving azithromycin and 49% of patients receiving amoxicillin failed to improve (P=0.567). Secondary: No differences in clinical failure or failure to improve were indicated in a per protocol analysis (children seen before day 11 after commencement of treatment). Azithromycin significantly reduced the proportion of children with nasal carriage of *S. pneumoniae* compared to amoxicillin (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Clinical and microbiological outcomes	
Feder et al.[61] (1999) Amoxicillin 750 mg orally daily for 10 days vs penicillin V 250 mg orally TID for 10 days	RCT, PRO Children with group A β-hemolytic streptococcal pharyngitis	N=152 14-21 day follow-up	Primary: Clinical course, bacteriologic eradication within 18-24 hours, bacteriologic treatment failure rate at day 4-6 and day 14-21	Primary: No significant differences between clinical response (about 90% for both groups, P=NS) or bacteriologic response at 18-24 hour follow-up visit (P=NS). Treatment failure occurred in 5% of the patients in the amoxicillin group and 11% of the patients in the penicillin V group.
Cohen et al.[62] (1996) Amoxicillin 50 mg/kg/day in two divided doses for 6 days vs penicillin V 45 mg/kg/day in three divided doses for 10 days	RCT, OL, MC Children with group A β-hemolytic streptococcal pharyngitis	N=318 1 month	Primary: Bacteriologic eradication at 4 days Secondary: Clinical efficacy, adverse events	Primary: Bacteriologic eradication at 4 days was similar between the amoxicillin and penicillin groups (83.7% vs 85.3%, P=0.71). Secondary: No significant differences in clinical efficacy were observed (clinical cure rate 90.8% for amoxicillin vs 89% for penicillin, P=NS). No serious adverse events were reported. Only 3 patients in the penicillin group discontinued treatment due to side effects.
Gopichand et al.[65] (1998) Amoxicillin 40 mg/kg/day TID for 10 days	RCT, SB, PRO Pediatric patients with group A streptococcal pharyngitis	N=113 10 days	Primary: Culture negativity at end of treatment Secondary: Resolution of	Primary: Amoxicillin was more likely to eradicate GAS than penicillin V (79.3% vs 54.5%, P=0.005). Secondary: Amoxicillin was more likely to resolve the symptoms than penicillin V

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs penicillin V 125-250 mg TID for 10 days			symptoms, adverse effects	(87.9% vs 70.9%, P=0.025). Two patients developed hives requiring discontinuation of penicillin V.
Addo-Yobo et al.[80] (2004) Amoxicillin 45 mg/kg orally in three divided doses vs penicillin G 200,000 units/kg/day in four divided doses	RCT, MC, OL Children 3 to 59 months of age who were hospitalized for severe pneumonia	N=1,702 Duration not specified	Primary: Treatment failure at 48 hours (clinical signs such as tachypnea, lower chest in-drawing) Secondary: Cumulative treatment failure at 5 and 14 days	Primary: Treatment failure rate for both groups was 19% at 48 hours. Secondary: Cumulative treatment failure rate was 22% for both groups at 5 days, and was 27% in the amoxicillin group and 26% in the penicillin group at 14 days (95% CI, -5% to 5%).
Atkinson et al.[111] (2007) Amoxicillin 8 mg/kg orally three times a day (children 6 months to 12 years) or 500 mg three times a day (children 12–16 years) vs penicillin benzyl 25 mg/kg IV four times a day (6 months	RCT, MC Children with community-acquired pneumonia	N=246 Variable duration	Primary: Time for the temperature to be <38 degrees C for 24 continuous hours and oxygen requirement to cease Secondary: Time in hospital, complications, duration of oxygen requirement and time to resolution of illness.	Primary: The time for temperature to settle and oxygen requirement to cease for those needing oxygen was similar in the two groups (1.3 days and 1.2 days in the IV and oral groups, respectively; P=0.03). Secondary: The median length of hospital stay was significantly shorter in the oral group than in the IV group (1.77 days and 2.1 days, respectively, P<0.001). The duration of oxygen requirement was significantly longer in the IV group than in the oral group (median 20.5 vs 11.0 hours, P=0.04). Three children in the oral group were changed to IV antibiotics and seven children in the IV group were changed to different IV antibiotics. Median time to complete resolution of symptoms was 9 days in both groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
to 16 years) Children in the IV group were changed to oral amoxicillin after a median of six IV doses and received 7 days of antibiotics in total.				
Lennon et al.[109] (2008) Amoxicillin 1,500 mg orally once daily (or 750 mg if <30 kg) for 10 days vs penicillin V 500 mg orally twice daily (or 250 mg if <20 kg) for 10 days	RCT Children with group A beta-hemolytic streptococcal (GABHS) pharyngitis	N=353 36 days	Primary: Eradication of GABHS	Primary: At visit 2 (days 3–6), the between treatment difference in the incidence of positive cultures was 0.3% with a bacteriological failure of 5.8% for amoxicillin and 6.2% for penicillin. At visit 3 (days 12–16), bacteriological failure was similar between groups (12.7% and 11.9% for amoxicillin and penicillin, respectively). At visit 4 (days 26–36), the incidence of positive cultures had increased with a between-treatment difference of 1.9% but bacteriological failure decreased slightly (10.7% for amoxicillin and 11.3% for penicillin V). There was no evidence of inferiority of amoxicillin to penicillin V at any time period. No significant differences in resolution of symptoms were noted between treatment groups.
Garau et al.[94] (2003) Amoxicillin-clavulanate extended-release tablets (XR) 2,000 mg/125 mg BID for 7-10 days	RCT, DB, DD, MC Patients ≥ 18 years of age with radiologically confirmed community-acquired pneumonia	N=230 7-10 days	Primary: Clinical response at follow-up (days 28-35) Secondary: Clinical response at end of therapy (days 9-14), bacteriological	Primary: Clinical success rate was higher in the amoxicillin-clavulanate XR group compared with the amoxicillin-clavulanate group (94.7% vs 88.8%; 95% CI, 1.1 to 13.0). Secondary: Radiological efficacy at follow-up was higher in the amoxicillin-clavulanate XR group compared with the amoxicillin-clavulanate group (94.7% vs 87.9%). Radiological success rates at the end of therapy were similar for both treatment groups (88.1% vs 86.7%; 95% CI, -6.8 to 9.5).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs amoxicillin-clavulanate 875 mg/125 mg TID for 7-10 days			response at end of therapy and at follow-up, radiological response at end of therapy and at follow-up, adverse events	Bacteriological success rate at follow-up was higher in the amoxicillin-clavulanate XR group compared with the amoxicillin-clavulanate group (85.0% vs 77.3%; 95% CI, 15.8 to 31.2). Adverse events were similar in both treatment groups.
File et al.[95] (2004) Amoxicillin-clavulanate XR 2,000 mg/125 mg BID for 7 days vs amoxicillin-clavulanate 875 mg/125 mg BID for 7 days	RCT, DB, PG, MC Patients ≥ 16 years of age with a clinical and radiological diagnosis of community-acquired pneumonia	N=633 7 days	Primary: Clinical response (sufficient improvement in the signs and symptoms of pneumonia) at follow-up (days 28-35) Secondary: Radiological outcome, bacterial response, adverse events	Primary: Clinical success rates were similar for both treatment groups (90.3% for amoxicillin-clavulanate XR vs 87.6% for amoxicillin-clavulanate; 95% CI, -3.0 to 8.3). Secondary: Bacteriological response rates were similar for both treatment groups at the end of therapy (90.5% for amoxicillin-clavulanate XR vs 82.5% for amoxicillin-clavulanate; 95% CI, -3.8 to 20.0) and at follow-up (86.6% vs 78.4%; 95% CI, -5.8 to 22.1). Radiological response rates at follow-up were also similar for both treatment groups (93.1% vs 90.3%; 95% CI, -2.1 to 7.8). Rates of adverse events reported were similar in both treatment groups (40.4% in the amoxicillin-clavulanate XR group vs 42.1% in the amoxicillin-clavulanate group).
Hazir et al.[110] (2008) Amoxicillin 80-90 mg/kg/day in two divided doses for 5 days (at home) vs ampicillin 100 mg/kg per day in	RCT, OL Children aged 3-59 months with severe pneumonia	N=2037 14 days	Primary: Treatment failure by day 6	Primary: There were 87 (8.6%) treatment failures in the hospitalized group and 77 (7.5%) in the ambulatory group (95% CI -1.3 to 3.5) by day 6. Five (0.2%) children died within 14 days of enrollment, one in the ambulatory group and four in the hospitalized group. In each case, treatment failure was declared before death and the antibiotic had been changed. None of the deaths were considered to be associated with treatment allocation. There were no serious adverse events reported in the trial.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
four doses for 48 hours (inpatient), followed by 3 days of oral amoxicillin 80-90 mg/kg/day				
Marple et al.[16] (2010) Amoxicillin-clavulanate 875 mg/125 mg every 12 hours for 10 days vs azithromycin extended-release 2 grams as a single dose	RCT, MC, OL Patients ≥18 years of age with acute bacterial maxillary sinusitis based on signs and symptoms lasting for 7 to 30 days	N=751 28 days	Primary: Symptom resolution at day 5 in the PP population Secondary: Time to resolution of symptoms, sinusitis-related quality of life, resource use, treatment success, and treatment satisfaction	Primary: At day 5 in the PP population, 29.7% of patients receiving azithromycin and 18.9% of patients receiving amoxicillin-clavulanate had symptom resolution (difference=10.8%; 95% CI, 3.1% to 18.4%). At day 5 in the ITT population, a significantly greater percentage of patients in the azithromycin group met the primary end point (20.0%) than in the amoxicillin-clavulanate group (13.2%; difference = 6.8%; 95% CI, 1.5% to 12.2%). Secondary: Over the course of the trial, both treatments led to similar rates of symptom resolution (HR, 1.16; 95% CI, 0.92 to 1.44). After 28 days, 67.4% of patients treated with azithromycin reported symptom resolution compared with 63.0% of patients receiving amoxicillin-clavulanate. There was no significant difference in mean reductions in SNOT-16 scores among the treatment groups at the first telephone interview and second interview in the PP population. In the PP population, 11.2% of patients reported receiving a prescription for a second antibiotic during the study period. The proportion of patients requiring additional antibiotics was similar in the azithromycin group (11.0%) and the amoxicillin-clavulanate group (11.3%). A similar number of patients reported unscheduled physician visits during the study in both treatment arms. Overall satisfaction with treatment was similar in the 2 treatment arms. Patients treated with azithromycin reported greater satisfaction with the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				convenience of the medication than did patients given amoxicillin-clavulanate (difference = 11.59; 95% CI, 8.78 to 14.40). Patients in the amoxicillin-clavulanate arm reported greater satisfaction with side effects than those treated with azithromycin (difference = −4.40; 95% CI, −8.13 to −0.66). More patients treated with azithromycin reported abdominal discomfort than did those receiving amoxicillin-clavulanate (70.76% vs 60.92%; P=0.02). There were no differences in reports of diarrhea among the treatment groups (P=0.50).
Arguedas et al.[18] (2011) Amoxicillin-clavulanate 45/3.2 mg/kg every 12 hours for 10 days vs azithromycin extended-release 60 mg/kg as a single dose	RCT, DB, MC Patients 3 to 48 months of age with acute otitis media	N=923 28 to 64 days	Primary: Clinical response at the test-of-cure (TOC) visit (days 12-14) in the bacteriologic eligible population Secondary: Bacterial response at other visits, compliance, and safety	Primary: Clinical response at the TOC visit was achieved in 80.5% of children in the azithromycin group compared to 84.5% in the amoxicillin-clavulanate group (difference – 3.9%; 95% CI, –10.4 to 2.6). Azithromycin was found to be non-inferior to amoxicillin-clavulanate. Secondary: The eradication rate across all ages was 82.6% in the azithromycin group and 92% in the amoxicillin-clavulanate group (P=0.050). Eradication rates were similar for *H. influenzae*, *M. catarrhalis* and S. *pyogenes*. Eradication rates were lower in the azithromycin group than in the amoxicillin-clavulanate group for *S. pneumoniae* (83.3% vs 97.9%; P=0.018). All penicillin-susceptible isolates were eradicated in both groups. All 11 penicillin-resistant *S. pneumoniae* isolates in the amoxicillin/clavulanate arm were eradicated. All patients receiving treatment with azithromycin received their single dose of active treatment; 59% of patients receiving amoxicillin-clavulanate received the full course of 20 doses. In the bacteriologic eligible population, 77% of patients in the amoxicillin-clavulanate arm were compliant with the full course of treatment compared with 100% of patients in the azithromycin group. Adverse events occurred in 56% of children treated with azithromycin ER and in 62.2% of children treated with amoxicillin-clavulanate. Most adverse events were of mild to moderate severity. Treatment-related vomiting was reported in 10.7% of patients receiving azithromycin and in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				8.2% of patients receiving amoxicillin-clavulanate.
Noel et al.[23] (2008) Amoxicillin-clavulanate (45 mg amoxicillin/kg) BID vs levofloxacin 10 mg/kg BID	RCT, MC, SB Children 6 months to 5 years of age with recurrent and/or persistent acute otitis media (AOM) that was unchanged or worsened after ≥3 days of treatment with an antimicrobial regimen used to treat AOM	N=1,650 27 days	Primary: Clinical cure rates at visit 3 (2-5 days post-therapy) Secondary: Clinical cure rate at visit 4 (10-17 days post therapy), clinical success (cured or improved) at visits 3 and 4, safety	Primary: Clinical cure rates were 72.4% with levofloxacin and 69.9% with amoxicillin-clavulanate (95% CI, -7.37 to 2.46). Levofloxacin was found to be non-inferior to amoxicillin-clavulanate. Cure rates were similar among different age groups: ≤24 months: 68.9% vs 66.2%, respectively (95% CI, -9.36 to 4.03); >24 months: 76.9% vs 75.1%; respectively (95% CI, -8.94 to 5.28). Secondary: Clinical cure rates at visit 4 were 74.9% for levofloxacin and 73.9% for amoxicillin-clavulanate (95% CI, -5.55 to 3.54). Clinical success rates at visit 3 were 94.0% for levofloxacin and 90.8% for amoxicillin-clavulanate (95% CI, -6.02 to -0.29). Clinical success rates at visit 4 were 83.6% for levofloxacin and 80.4% for amoxicillin-clavulanate (95% CI, -7.18 to 0.81). There was no difference observed between treatments regarding frequency or type of adverse events. Most adverse events were mild or moderate in severity (97% levofloxacin; 96% amoxicillin-clavulanate) with diarrhea being the most frequent.
Thomsen et al.[59] (1997) Amoxicillin-clavulanate 12.5 mg/3.125 mg orally BID for 14 days vs amoxicillin-clavulanate 12.5	RCT, DB, PRO Children 1 to 10 years of age with secretory otitis media of at least 3 months duration	N=360 2 months after initiation of therapy	Primary: Improved tympanometric findings at 14 and 28 days after start of therapy	Primary: Amoxicillin-clavulanate treatment for 28 days was significantly more efficacious than amoxicillin-clavulanate for 14 days (P=0.07), penicillin V for 14 days (P=0.005), and penicillin V for 28 days (P<0.001) at improving tympanometric testing (44%, 31%, 23%, 19%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/3.125 mg orally BID for 28 days vs penicillin V 25 mg orally BID for 14 days vs penicillin V 25 mg orally BID for 28 days				
Brook et al.[66] (1989) Amoxicillin-clavulanate 40 mg/kg/day in four divided doses for 10 days vs penicillin VK 40 mg/kg/day in four divided doses for 10 days	PRO, RCT, DB Children 4 to 16 years of age with acute recurrent group A β-hemolytic streptococcal tonsil-litis (>2 episodes per year) despite prior treatment with antibiotics for 10 days (penicillin or erythromycin)	N=43 Up to 1 year	Primary: GAS eradication 10 days post-therapy Secondary: Recurrence of tonsillitis in 1 year	Primary: Amoxicillin-clavulanate eradicated GAS more effectively than penicillin VK (100% vs 70%, P<0.001). Secondary: Amoxicillin-clavulanate prevented recurrent tonsillitis more effectively than penicillin VK (89% vs 42%, *P* < 0.005).
Syrogiannopoulos et al.[64] (2004) Amoxicillin-clavulanate 43.8/6.2	RCT, OL, MC Children 2 to 16 years of age with Group A streptococcal (GAS) tonsillo-pharyngitis	N=537 5-10 days	Primary: Microbiologic eradication of GAS at 4-8 days post-therapy Secondary:	Primary: Amoxicillin-clavulanate and penicillin V were comparable (85% vs 84%, P=NS), but were more efficacious than lower and higher dose clarithromycin (59%, 61%, P<0.05) in the eradication of GAS 4-8 days post-therapy. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/kg/day in two divided doses for 5 days vs penicillin V 30 mg/kg/day every 8 hours for 10 days vs clarithromycin 15 mg/kg/day in two divided doses for 5 days vs clarithromycin 30 mg/kg/day in two divided doses for 5 days			microbiologic eradication at 21-28 days post-therapy, clinical response at 4-8 days post-therapy, tolerance	Amoxicillin and penicillin V were comparable (83% vs 77%, P=NS), but showed a higher GAS eradication rate than lower dose clarithromycin (60%, P<0.05) at 21-28 days post-therapy. Furthermore, amoxicillin-clavulanate was more effective than higher dose clarithromycin (66%, P<0.05). No difference in clinical response rate 4-8 days post-therapy (96% with higher dose clarithromycin, 94% with lower dose clarithromycin, 97% with amoxicillin-clavulanate, 98% with penicillin V, P=NS). There was a trend toward lower clinical response with lower dose clarithromycin at 21-28 days (94%, 89%, 94%, 95%, P=0.1). Adverse events were similar in number and severity across all treatment groups; one patient in the amoxicillin-clavulanate group discontinued treatment for diarrhea and one patient in the penicillin group discontinued therapy for rash.
Siempos et al.[112] (2007) Amoxicillin-clavulanate (A/C) vs macrolides vs quinolones	MA Patients >18 years old with acute bacterial exacerbation of chronic bronchitis (ABECB)	N=7,405 (19 RCT) 26 weeks	Primary: Treatment success, hospitalization, mortality, adverse events	Primary: There was no difference regarding treatment success in intention-to-treat and clinically evaluable patients between macrolides and quinolones, A/C and quinolones, or A/C and macrolides. The treatment success in microbiologically evaluable patients was lower for macrolides compared with quinolones (OR 0.47, 95% CI, 0.31-0.69). There was no difference in the need for hospitalization for patients treated with macrolides compared with patients treated with quinolones (OR 1.37; 95% CI, 0.75 – 2.5). Data regarding need for hospitalization were only available in two trials comparing A/C with quinolones, and in one trial comparing A/C with macrolides.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no difference in mortality between macrolide-treated patients with ABECB and those treated with quinolones (OR 1.96, 95% CI 0.45–8.51). Data on mortality were provided in only two trials comparing A/C with quinolones. Fewer quinolone-recipients experienced a recurrence of ABECB after resolution of the initial episode compared with macrolide-recipients during the 26-week period following therapy. Adverse effects in general were similar between macrolides and quinolones. Administration of A/C was associated with more adverse effects than quinolones (OR 1.36, 95% CI 1.01-1.85).
Feder et al.[57] (1982) Ampicillin 70 mg/kg in four divided doses for 10 days vs amoxicillin 30 mg/kg in three divided doses for 10 days vs sulfamethoxazole-trimethoprim (SMX-TMP) 7.5/37.5 mg/kg in two divided doses for 10 days	RCT, DB Children 2 months to 7 years of age with acute otitis media	N=263 14 days	Primary: Tolerability (discontinuation rate) Secondary: Efficacy (days to resolution of symptoms, eardrum mobility improvement at day 14)	Primary: Ampicillin was less well tolerated than amoxicillin and SMX-TMP (discontinuation rate 7.2%, 0%, 1.1%, P<0.05). Secondary: Symptoms resolved in all groups in less than 2 days, eardrum mobility improved with ampicillin (58%), amoxicillin (63%), and SMX-TMP (70%).
Mackay et al.[82] (1980)	RCT, DB, MC	N=199	Primary: Clinical response	Primary: There was no significant difference between any of the treatment groups in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ampicillin 250 mg orally TID for 7 days vs ampicillin 500 mg orally TID for 7 days vs amoxicillin 250 mg orally TID for 7 days vs amoxicillin 500 mg orally TID for 7 days	Patients with acute exacerbations of chronic bronchitis	7 days	(no indication for continued antibiotics), days for sputum to become mucoid	clinical response (70%, 74%, 62%, 74%, P=NS) or in days for sputum to become mucoid (5.1, 5.2, 5.0, 5.0, P=NS).
Seki et al.[30] (2009) Ampicillin-sulbactam 3 g IV twice daily for 7 to 14 days (SBT/ABPC) vs piperacillin 2 g IV twice daily for 7 to 14 days (PIPC)	RCT Patients with mild to severe community-acquired pneumonia	N=109 7 to 14 days	Primary: Efficacy and safety	Primary: The total efficacy rate was 77.4% in the PIPC group and 67.3% in the SBT/ABPC group. There was no significant difference among the treatment groups. There was a significant difference in efficiency between PIPC and SBT/ABPC treatments in male patients (79.4% vs 55.6%, respectively; P<0.046), and patients with underlying disease (83.3% vs 57.6%, respectively; P<0.019), and in respiratory disease patients (84.6% vs 28.6%, respectively; P<0.022). There was also a significant difference in efficiency among SBT/ABPC groups dependent on age. In the PIPC group, adverse reactions were seen in 5.4% of patients and the major adverse reactions were diarrhea and hepatic dysfunction. In the SBT/ABPC group, adverse reactions were seen in 9.4% of the patients,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				with the major adverse reactions being diarrhea and hepatic dysfunction. No significant differences were found between the groups. All reactions were mild or moderate and transient.
Allewelt et al.[96] (2004) Ampicillin-sulbactam vs clindamycin with or without cephalosporin Dosing varied per patient	RCT, OL PRO, MC Patients with aspiration pneumonia and lung abscess	N=70 Mean 23.4 days	Primary: Clinical response	Primary: Clinical response at end of therapy in the ampicillin-sulbactam group was 73% vs 66.7% in the clindamycin group (P values were 0.06 and 0.02). Clinical response at 7 to 14 days after therapy was 65.7% in the ampicillin-sulbactam group vs 63.5% in the clindamycin group (P values were 0.10 and 0.04). Duration of therapy was 22.7 days in the ampicillin-sulbactam group vs 24.1 days in the clindamycin group.
Peyramond et al.[63] (1996) Penicillin V 1 million units TID for 10 days vs amoxicillin 1 g BID for 6 days	RCT, PRO, OL, MC Patients with Group A β-hemolytic streptococcal (GABHS) acute tonsillitis	N= 234 1 month posttreatment follow-up	Primary: GABHS eradication Secondary: Clinical efficacy, adverse effects	Primary: Successful GABHS eradication was similar between the two treatment groups at end of treatment (92% for amoxicillin vs penicillin V 92.7%, P=0.95) and at 1 month posttreatment (90.8% vs 92.6%, P=0.85). Secondary: Clinical response rates were similar between the two groups at end of treatment (96% for amoxicillin vs 95.4% for penicillin, P=0.92) and at one month (91.7% vs 94.7%, P=0.59). Adverse effects occurred in 3% of patients in the amoxicillin group and 5.2% of the patients in the penicillin group, with 3 patients in the penicillin group requiring discontinuation of treatment.
Curtin-Wirt et al.[67] (2003) Penicillin V 35 mg/kg/day in two divided doses	PRO, OL, OBS Children with group A β-hemolytic streptococcal tonsillo-pharyngitis	N=276 6-14 day posttreatment	Primary: Bacteriologic cure rate Secondary: Clinical cure rate	Primary: Bacteriologic cure rate was 76% in the amoxicillin group vs 64% in the penicillin group (P=0.04). Secondary: Clinical cure rate was 84% in the amoxicillin group vs 73% in the penicillin group (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs amoxicillin 35 mg/kg/day in two divided doses				
Bansal et al.[78] (2006) Penicillin 50,000 units/kg IV every 6 hours plus gentamicin 2.5 mg/kg IV every 8 hours, then amoxicillin 15 mg/kg orally every 8 hours vs amoxicillin-clavulanate 30 mg/kg IV every 12 hours then orally	RCT, OL Children 2 to 59 months of age hospitalized with severe hypoxemic pneumonia	N=71 Duration not specified	Primary: Treatment failure (change in antibiotic regimen due to worsening clinical status) Secondary: Mean duration of intravenous antibiotics	Primary: Treatment failure rate was similar in both groups (2.6% with penicillin and 3% with amoxicillin-clavulanate). Secondary: Mean duration of intravenous antibiotics was similar in both groups (76 h vs 75 hours).
Gaillat et al.[79] (1994) Penicillin 3 million units every 6 hours plus ofloxacin 200 mg BID vs amoxicillin-clavulanate 1g every 6 hours plus	RCT, PRO, MC Hospitalized patients with severe community-acquired pneumonia	N=117 30 days	Primary: Clinical improvement at completion of therapy, clinical recovery 30 days after therapy started Secondary: Mortality, tolerance	Primary: Mean duration of treatment was similar between penicillin/ofloxacin and amoxicillin-clavulanate/erythromycin groups (13.4 days vs 15.1 days). Clinical improvement (76.9% vs 76%), mortality (5.9% vs 5.9%), and recovery at follow-up (97% vs 94.4%) were similar for both groups (P=NS for all variables). Secondary: Six patients (10.3%) in each treatment group died of the infection. Adverse effects were seen in four patients in penicillin group and nineteen patients in amoxicillin-clavulanate group (of which five patients required

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
erythromycin 1 g every 8 hours				discontinuation of the antibiotic). Erythromycin was associated with a higher incidence of thrombophlebitis.
Joshi et al.[97] (1999) Piperacillin-tazobactam 3.375 g every 4 hours plus tobramycin 5 mg/kg/day divided every 8 hours vs ceftazidime 2 g every 8 hours plus tobramycin 5 mg/kg/day divided every 8 hours	RCT, OL, MC Patients with nosocomial lower respiratory tract infection	N=136 Duration not specified	Primary: Clinical response	Primary: Clinical success rate was 74% in the piperacillin-tazobactam group vs 50% in the ceftazidime group (P=0.006). Eradication rate of baseline pathogen was 66% in the piperacillin-tazobactam group vs 38% in the ceftazidime group (P=0.003). Mortality rate in the piperacillin-tazobactam group was 7.7% vs 17% in the ceftazidime group (P=0.03).
Brun-Buisson et al.[98] (1998) Piperacillin-tazobactam 4.5 g QID plus amikacin 7.5 mg/kg BID vs ceftazidime 1 g QID plus amikacin 7.5 mg/kg BID	OL, MC, RCT Patients with ventilator-associated pneumonia	N=115 Duration not specified	Primary: Clinical response	Primary: Bacteriologically-confirmed infections included polymicrobial infections (37%) and those involving *P aeruginosa* (32%). Clinical cure rate was 51% in the piperacillin-tazobactam arm vs 36%in the ceftazidime arm (95% CI, -0.2 to 30.2%). 28-day mortality rate was 16% in the piperacillin-tazobactam arm vs 20% in the ceftazidime arm (P=0.55). Bacteriologic failure rate was 33% with piperacillin-tazobactam + amikacin vs 51% with ceftazidime + amikacin (P=0.05).
Ito et al.[27] (2010) Piperacillin-	RCT, OL, SC Patients aged ≥15 years of age with a	N=469 30 days	Primary: Clinical response rate at the end of treatment (EOT) in	Primary: At the EOT visit, the clinical effective rate for the VPP population was 83% for TAZ/PIPC and 82% for IPM/CS (P=0.92).

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tazobactam 5 g IV every 12 hours for 7 to 14 days (TAZ/PIPC) vs imipenem-cilastatin 1 g IV every 12 hours for 7 to 14 days (IPM/CS)	risk for aspiration who had been hospitalized after developing moderate-to-severe pneumonia in the community or nursing home		validated per protocol (VPP) population Secondary: Clinical response during treatment (days 4 and 7) and at the end of study (EOS) in VPP population, and survival at day 30 in modified intention-to-treat (MITT) population	Secondary: There were no significant differences between the groups in any of the secondary outcome measures. Mortality rate within 30 days of admission in MITT population was 15% in the TAZ/PIPC group and 24% in the IPM/CS group (P=0.12). The most frequent adverse event was diarrhea in both groups, affecting 28% of patients receiving TAZ/PIPC and 31% of patients receiving IPM/CS.
Miscellaneous Infections				
Kacmar et al.[89] (2001) Amoxicillin 500 mg TID for 7 days vs azithromycin 1 g single dose	RCT, SB Women with *C trachomatis* in pregnancy before 33 weeks gestation	N=39 4-6 weeks post-therapy	Primary: Clinical response	Primary: No statistically significant differences in side effects, compliance, or efficacy were observed between the two treatment groups.
Gupta et al.[22] (2009) Amoxicillin-clavulanate 12.5 mg/kg orally every 8 hours and ofloxacin 7.5 mg/kg orally every 12 hours as outpatient therapy	RCT, SC, OL Pediatric patients 2 to 15 years of age with low-risk febrile neutropenia (LRFN)	N=88 (123 febrile episodes) Variable duration	Primary: Treatment success	Primary: In the per protocol analysis, treatment was successful in 90.16% of episodes in the oral group and in 93.10% of episodes in the intravenous group. In the ITT analysis, the success rate was 88.7% in the oral group and 88.5% in the intravenous group (P=0.97). There were 3 hospitalizations (all in the oral group) and no mortality.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ceftriaxone 75 mg/kg/day IV and amikacin 15 mg/kg once daily as outpatient therapy				
Innes et al.[104] (2003) Amoxicillin-clavulanate 500/175 mg every 8 hours plus ciprofloxacin 750 mg BID for 5 days vs gentamicin 80 mg every 8 hours plus piperacillin-tazobactam 4.5 g every 8 hours until hospital discharge	RCT, PRO Patients with low-risk febrile neutropenia	N=126 3 days (mean duration)	Primary: Clinical response	Primary: Initial treatment was successful without antibiotic modification in 90% of piperacillin-tazobactam plus gentamicin arm vs 84.8% in the amoxicillin-clavulanate plus ciprofloxacin arm (P=0.55). Median patient stay was 4 days in the piperacillin-tazobactam plus gentamicin arm vs 2 days in the amoxicillin-clavulanate plus ciprofloxacin arm (P<0.0005).
Metsvaht et al.[31] (2010) Ampicillin 25 mg/kg every 8 to 12 hours and gentamicin 4 to 5 mg/kg every 24 to 48 hours (AMP) vs	RCT, OL Neonates admitted within 72 hours of life, needing early empiric antibiotic treatment for early onset sepsis (EOS) or risk factors of infection	N=283 Variable duration	Primary: Treatment failure Secondary: Mortality, duration of early empiric antibiotic therapy, duration of respiratory support and vasoactive treatment, rate of	Primary: The overall treatment failure rates (14.2% in PEN vs 14.1% in AMP group) as well as the proportions of the individual components of the primary endpoint were similar in both arms. There were almost identical treatment success rates for both treatment regimens (P=0.92). Secondary: Both treatment arms were equal with regards to the secondary endpoints. The overall incidence of proven EOS was 4.9%. Among neonates receiving AMP or PEN, change of antibiotic regimen within 72 hours

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
penicillin G 25,000 IU/kg every 8 to 12 hours and gentamicin 4 to 5 mg/kg every 24 to 48 hours (PEN)			LOS and use of additional antibacterial therapy	(10/142 vs 10/141; OR 1.02; 95% CI, 0.40–2.59), 7-day mortality (11/142 vs 14/141; OR 0.76; 95% CI, 0.33–1.75) and over-all treatment failure (20/142 vs 20/141; OR 1.01; 95% CI, 0.52–1.97) occurred at similar rates.
Ziogos et al.[19] (2010) Ampicillin-sulbactam 3 g IV as a single dose vs cefuroxime 1.5 g IV as a single dose	RCT Women scheduled for cesarean delivery	N=176 30 days	Primary: Development of an infection	Primary: Postoperative infections developed in 5.9% of patients receiving cefuroxime and 8.8% of patients receiving ampicillin-sulbactam (P=0.6). In univariate analyses 6 or more vaginal examinations prior to the operation (P=0.004), membrane rupture for more than 6 hours (P=0.08) and blood loss greater than 500 ml (P=0.018) were associated with developing a postoperative surgical site infection (SSI). In logistic regression having 6 or more vaginal examinations was the most significant risk factor for a postoperative SSI (OR 6.8; 95% CI, 1.4 to 33.4; P=0.019). Regular prenatal follow-up was associated with a protective effect (OR 0.04; 95% CI, 0.005-0.36; P=0.004). Patients that developed an infection had a lengthier hospital stay (median of 5 vs 4 days; P<0.001). All patients with an infection responded well to subsequent antibiotics. No adverse drug reactions were reported.
McKinnon et al.[101] (1999) Ampicillin-sulbactam 1.5 or 3.0 g every 6 hours vs ticarcillin-clavulanate 3.1 g	RETRO, OL, MC Patients with skin and soft tissue, intraabdominal, gynecologic, respiratory, urinary tract, or other infections requiring parenteral antibiotic therapy	N=890 Duration not specified	Primary: Clinical response rate Secondary: Bacteriologic cure rate	Primary: Rate of satisfactory clinical response was highest with ampicillin-sulbactam 1.5 g (85.9% vs 82.5% for ampicillin-sulbactam 3.0 g vs 77.5% for ticarcillin-clavulanate, P=0.044). Secondary: Overall bacteriologic efficacy of ampicillin-sulbactam and ticarcillin-clavulanate were not statistically different, with the exception of a higher bacteriologic eradication rate for ticarcillin-clavulanate against *Pseudomonas* species (P=0.013).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
every 6 hours				
Gentry et al.[84] (1997) Nafcillin vs vancomycin	RETRO Patients with staphylococcal endocarditis	N=56 Duration not specified	Primary: Clinical response	Primary: In patients with methicillin-sensitive *Staphylococcus aureus* infection, complete response rate was 74% in the nafcillin group compared with 50% in the vancomycin group (P=0.12); however these differences were not statistically significant. Mortality rate was 22% in the nafcillin group and 28% in the vancomycin group (P=0.73).
Heldman et al.[83] (1996) Oxacillin 2 g every 4 hours or vancomycin 1 g every 12 hours plus gentamicin 2 mg/kg every 8 hours (IV arm) vs ciprofloxacin 750 mg BID orally plus rifampin 300 mg BID orally (oral arm)	RCT, PRO Patients with staphylococcal endocarditis and history of injection drug use	N=85 28 days	Primary: Clinical response	Primary: Observed cure rate was higher in the oral arm (95% vs 88%, P=0.6); however, this difference was not statistically significant. Drug toxicity was higher with the IV arm (2.8% vs 61.5, P<0.001). Oxacillin-induced hepatotoxicity (33.3% of IV arm) prompted a change in therapy to vancomycin.
Fang et al.[102] (1998) Piperacillin 4 g-tazobactam 500 mg every 8 hours by intravenous infusion vs	RCT, OL Hospitalized patients 16 years and older with lower respiratory tract infections or urinary tract infections	N=124 7-14 days	Primary: Overall clinical efficacy rates, bacterial eradication rates Secondary: Adverse events	Primary: No statistical differences were observed between the two groups. Overall efficacy rates for the treatment of all infections was 90.5% in the piperacillin-tazobactam group compared with 88.5% in the ticarcillin-clavulanate group (P>0.05). Bacterial clearance rates for the piperacillin-tazobactam group were 90.2% versus 92.0% for the ticarcillin-clavulanate group (P>0.05). Secondary: Adverse drug reactions were similar in both groups (7.69% for ticarcillin-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ticarcillin 3 g-clavulanate 200 mg every 8 hours by intravenous infusion				clavulanate vs 8.06% for piperacillin-tazobactam, P=0.938).
Kobayashi et al.[113] (2009) Piperacillin-tazobactam 125 mg/kg/day plus ceftazidime 100 mg/kg/day divided into 4 doses (PIPC/TAZ+CAZ) vs ampicillin-sulbactam 150 mg/kg/day plus aztreonam 150 mg/kg/day divided into 4 doses (SBT-ABPC+AZT) Treatment was continued until completion of the appropriate course of therapy for a defined clinical or microbiologic infection.	RCT Pediatric patients with hematologic disease and solid tumor with febrile neutropenia	N=54 (177 episodes) 120 hours	Primary: Treatment success	Primary: Success rates were 57.1% and 62.5% in the PIPC/TAZ+CAZ and SBT/ABPC+AZT groups, respectively (P≥0.05). There were 2 deaths in the PIPC/TAZ+CAZ group. The patients died within 48 hours from onset of the febrile episode. The success rates in episodes with absolute neutrophil counts <0.5x10^9/L at the end of treatment were 70.0% and 74.1% in the PIPC/TAZ+CAZ and SBT-ABPC+AZT groups, respectively, and the success rates in bacteremia episodes were 50% in both groups. The percentages of episodes with new infections were 25.7% and 20.3%, respectively. Duration of fever and antibiotic therapy did not differ between the groups, and no major adverse effects occurred in the study.
Uygun et al.[21] (2009)	RCT, OL	N=70 (131 episodes)	Primary: Success	Primary: Success without modification was similar between the two groups (60.0%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Piperacillin-tazobactam 80 mg/kg-10 mg/kg IV every 6 hours (PIP/TAZO) vs cefepime 50 mg/kg IV every 8 hours (CEF)	Patients ≤19 years of age who had been treated for hematological malignancies or solid tumors and had febrile neutropenia	Variable duration	without modification	vs 61.3% for PIP/TAZO and CEF, respectively; P>0.05). Success without modification was 84.8% and 92.1% for PIP/TAZO and CEF treatments, respectively, in patients with fever of unknown origin (FUO) episodes. Success without modification was 29.2% and 12.5% in microbiologically documented infection episodes (P>0.05). Modifications were done with only glycopeptides in 8 episodes, only antifungals in 20 episodes, only carbapenems in 11 episodes, and only antiprotozoals in 2 episodes. Duration of fever and neutropenia was similar in both groups. There was no significant difference in the duration of hospitalization between the treatment groups. No treatment changes were made because of potential side or adverse effect of PIP/TAZO or CEF. The most frequent adverse events were rash (7.7% in PIP/TAZO and 6.4% in CEF) and diarrhea (6.1% in PIP/TAZO and 6.4% in CEF).
Gómez et al.[20] (2010) Piperacillin-tazobactam 4 g/500 mg IV every 8 hours plus amikacin 15 mg/kg/day as a single dose (PT-A) vs cefepime 2 g IV every 12 hours plus amikacin 15 mg/kg/day as a	RCT, OL Patients >18 years of age with febrile neutropenia	N=190 (317 episodes) Variable duration	Primary: Clinical efficacy and toxicity	Primary: The antibiotic success rate (no change or addition of antibiotics) was recorded in 59% of episodes in the C-A group and in 64% of episodes in the PT-A group (P=NS). Resolution of the febrile episode (with or without change in therapy) was observed in 92% of episodes in the C-A group and in 92% of episodes in the PT-A group. The 28-day mortality (all-cause) was similar in both groups: 9.9% in the C-A group and 10.5% in the PT-A group (P=NS). A microbiologically documented infection was present in 35% of episodes in the C-A group and 25% of episodes in the PT-A group (P=NS). A clinically documented infection was observed in 26% of episodes in the C-A group and 28% of episodes in the PT-A group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
single dose (C-A)				Toxicity was observed in 4% of episodes in the C-A group and in 3% of episodes in the PT-A group.
Philpott-Howard et al.[106] (2003) Piperacillin-tazobactam 4.5 g TID vs ciprofloxacin 400 mg BID plus amoxicillin 500 mg TID with or without metronidazole	RCT, PRO Patients with infections after liver transplantation	N=217 3 months	Primary: Clinical response (improvement in symptoms of infection)	Primary: At 72 hours, overall response rate was 66.1% in the piperacillin-tazobactam group vs 60% in the ciprofloxacin and amoxicillin group (P=0.399). At the end of the study, successful clinical outcome was observed in 58.9% of patients in the piperacillin-tazobactam group vs 50.5% in the ciprofloxacin and amoxicillin group (P=0.222).
Vural et al.[25] (2010) Piperacillin-tazobactam 360 mg/kg/day IV in four divided doses vs imipenem-cilastatin 60 mg/kg/day IV in four divided doses	RCT Patients with acute leukemia, lymphoma and solid tumors who were hospitalized with febrile neutropenia	N=63 (99 episodes) Variable duration	Primary: Success and failure rate	Primary: The overall success rate was 67% and the failure rate was 33% in both treatment groups. The success and failure rates in the piperacillin–tazobactam group were 71% and 29%, respectively. The success and failure rates in the imipenem–cilastatin group were 62% and 38%, respectively (P>0.05 vs piperacillin-tazobactam). There were no deaths in the study and no major adverse effects were seen in either group. Mild adverse effects included nausea, vomiting, transient increase in liver function tests and rash. No patient required discontinuation of the therapy due to adverse effects.
Petrilli et al.[105] (2003)	RCT, PRO, OL Pediatric patients	N=70 Duration	Primary: Clinical response (resolution of	Primary: Overall successful response to therapy was not significantly different between treatment arms (93.0% for C+A vs 96.0% for TC, P=0.716).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ticarcillin-clavulanate (TC) 250 mg/kg/day in four doses IV vs ceftriaxone 100 mg/kg/day plus amikacin 15 mg/kg/day (C+A) BID IV	with leukemia or lymphoma, who developed fever and neutropenia (defined as absolute neutrophil count <500 cells/mm^3) during chemotherapy	varied	neutropenia or completion of an appropriate course of therapy for a defined clinical or microbiological infection) Secondary: Adverse events	Duration of neutropenia was not statistically different between treatment arms (7.6 days in C+A group vs 8.7 days in TC group, P=0.332). Secondary: Rates of adverse events were similar in both groups (P=1.000).

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PM=post marketing, PRO=prospective, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, TB=triple-blind, XO=crossover

Additional Evidence

Dose Simplification
Previous analyses have demonstrated that oral antibiotics given once or twice daily are associated with higher adherence rates than antibiotics given three times daily.[24,29] Thanaviratananich et al. conducted a systematic review to evaluate clinical cure rates with amoxicillin (with or without clavulanate) administered once or twice daily compared to three times daily.[108] Five studies involving 1,601 patients were included. All studies were found to be at moderate to high risk for bias; therefore, the investigators did not perform a pooled data meta-analysis. The clinical cure rates at the end of therapy and at the follow-up periods of each study were shown to be comparable between the two groups.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 14. Relative Cost of the Penicillins

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amoxicillin	capsule, chewable tablet, extended-release tablet, suspension, tablet	Moxatag®	$$$$	$
Amoxicillin and clavulanate	chewable tablet, extended-release tablet, suspension, tablet	Augmentin®*, Augmentin XR®*	$$-$$$$	$-$$$
Ampicillin	capsule, injection, suspension	N/A	N/A	$-$$$$$
Ampicillin and sulbactam	injection	Unasyn®*	$$$$-$$$$$	$$$-$$$$
Dicloxacillin	capsule	N/A	N/A	$
Nafcillin	injection	N/A	N/A	$$$-$$$$$
Oxacillin	injection	N/A	N/A	$$$$$
Penicillin G benzathine	injection	Bicillin L-A®	$$$-$$$$	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Penicillin G benzathine and penicillin G procaine	injection	Bicillin C-R®	$$	N/A
Penicillin G potassium	injection	Pfizerpen®*	$$$$	$$$-$$$$
Penicillin G procaine	injection	N/A	N/A	$
Penicillin G sodium	injection	N/A	N/A	$$$$$
Penicillin V potassium	suspension, tablet	N/A	N/A	$
Piperacillin and tazobactam	injection	Zosyn®*	$$$$-$$$$$	$$$$$
Ticarcillin and clavulanate	injection	Timentin®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The penicillins are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-12] They are classified into five groups based on their spectrum of activity, including natural penicillins, penicillinase-resistant penicillins, aminopenicillins, carboxypenicillins, and ureidopenicillins. The majority of the penicillins are available in a generic formulation. There is at least one oral and one injectable agent available in a generic formulation within each subgroup, with the exception of ticarcillin/clavulanate.

There are many guidelines that define the appropriate place in therapy for the penicillins. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the penicillin. The penicillins are recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, encephalitis, meningitis, skin and soft-tissue infections, *Helicobacter pylori* infections, syphilis, pyelonephritis, otitis media, pharyngitis, sinusitis, anthrax, infectious exacerbations of COPD, community-acquired pneumonia, nosocomial pneumonia, intra-abdominal infections, Lyme disease, as well as for the prophylaxis for rheumatic fever.[33-41,44-51,53-56,115-118,120] They are recommended as an alternative treatment option for pelvic inflammatory disease and cystitis.[41,43-44]

Clinical trials have demonstrated comparable efficacy among the penicillins for the treatment of skin and soft-tissue infections, genitourinary infections, upper/lower respiratory tract infections, as well as several miscellaneous infections.[30-31,58,60-64,70-72,74,78-82,85-87,90-91,102,104,107,110-111,113] The penicillins have also been shown to be comparable in efficacy to antibacterial agents in other classes.[15,17-23,25-28,32,69,84,89,92-93,98,100,103,105-106,112] Clinical data from published studies supports similar safety profiles among the penicillins.

There is insufficient evidence to support that one brand penicillin is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand penicillins within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand penicillin is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2011. Available from Wolters Kluwer Health, Inc. Accessed November 2011.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2011; November 2011.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November 2011.
4. Moxatag® [packet insert]. San Diego, CA: Victory Pharma, Inc.; January 2011.
5. Augmentin® [package insert]. Bridgewater, NJ: Dr. Reddy's Laboratories, Inc.; September 2011.
6. Augmentin XR® [package insert]. Bridgewater, NJ: Dr. Reddy's Laboratories, Inc.; August 2011.
7. Unasyn® [package insert]. New York, NY: Pfizer, Inc.; April 2007.
8. Bicillin® C-R [package insert]. Bristol, TN: King Pharmaceuticals, Inc.; September 2009.
9. Bicillin® L-A [package insert]. Bristol, TN: King Pharmaceuticals, Inc.; September 2009.
10. Pfizerpen® [package insert]. New York, NY: Pfizer; December 2005.
11. Zosyn® [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc; April 2011.
12. Timentin® [packet insert]. Research Triangle Park, NC: GlaxoSmithKline; June 2011.
13. Mandell GL, Bennett JE, Dolin R. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 6th ed. Philadelphia, PA, Elsevier ; 2005.
14. Calderwood SB. Penicillins. In: UpToDate, Hooper, DC (Ed), UpToDate, Waltham, MA, 2011.
15. Hook EW 3rd, Behets F, Van Damme K, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. J Infect Dis 2010;201:1729-35.
16. Marple BF, Roberts CS, Frytak JR, et al. Azithromycin extended release vs amoxicillin/clavulanate: symptom resolution in acute sinusitis. Am J Otolaryngol 2010;31:1-8.
17. Morris PS, Gadil G, McCallum GB, et al. Single-dose azithromycin versus seven days of amoxycillin in the treatment of acute otitis media in Aboriginal children (AATAAC): a double blind, randomised controlled trial. Med J Aust 2010;192:24-9.
18. Arguedas A, Soley C, Kamicker BJ, et al. Single-dose extended-release azithromycin versus a 10-day regimen of amoxicillin/clavulanate for the treatment of children with acute otitis media. Int J Infect Dis 2011;15:e240-8.
19. Ziogos E, Tsiodras S, Matalliotakis I, et al. Ampicillin/sulbactam versus cefuroxime as antimicrobial prophylaxis for cesarean delivery: a randomized study. BMC Infect Dis 2010;10:341.
20. Gómez L, Estrada C, Gómez I, et al. Low-dose beta-lactam plus amikacin in febrile neutropenia: cefepime vs piperacillin/tazobactam, a randomized trial. Eur J Clin Microbiol Infect Dis 2010;24:417-27.
21. Uygun V, Karasu GT, Ogunc D, et al. Piperacillin/tazobactam versus cefepime for the empirical treatment of pediatric cancer patients with neutropenia and fever: a randomized and open-label study. Pediatr Blood Cancer 2009;53:610-4.
22. Gupta A, Swaroop C, Agarwala S, et al. Randomized controlled trial comparing oral amoxicillin-clavulanate and ofloxacin with intravenous ceftriaxone and amikacin as outpatient therapy in pediatric low-risk febrile neutropenia. J Pediatr Hematol Oncol 2009;31:635-41.
23. Noel GJ, Blumer JL, Pichichero ME, et al. A randomized comparative study of levofloxacin versus amoxicillin/clavulanate for treatment of infants and young children with recurrent or persistent acute otitis media. Pediatr Infect Dis J 2008;27:483-9.
24. Pechere J, Hughes D, Kardas P, et al. Non-compliance with antibiotic therapy for acute community infections: a global survey. International Journal of Antimicrobial Agents 2007;29:245–53.
25. Vural S, Erdem E, Gulec SG, et al. Imipenem-cilastatin versus piperacillin-tazobactam as monotherapy in febrile neutropenia. Pediatr Int 2010;52:262-7.
26. Saltoglu N, Dalkiran A, Tetiker T, et al. Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital. Clin Microbiol Infect 2010;16:1252-7.
27. Ito I, Kadowaki S, Tanabe N, et al. Tazobactam/piperacillin for moderate-to-severe pneumonia in patients with risk for aspiration: comparison with imipenem/cilastatin. Pulm Pharmacol Ther 2010;23:403-10.
28. Tong SY, Andrews RM, Kearns T, et al. Trimethopim-sulfamethoxazole compared with benzathine penicillin for treatment of impetigo in Aboriginal children: a pilot randomised controlled trial. J Paediatr Child Health 2010;46:131-3.
29. Kardas P. Comparison of patient compliance with once-daily and twice-daily antibiotic regimens in respiratory tract infections: results of a randomized trial. Journal of Antimicrobial Chemotherapy 2007;59:531–6.

30. Seki M, Higashiyama Y, Imamura Y, et al. A clinical comparative study of piperacillin and sulbactam/ampicillin in patients with community-acquired bacterial pneumonia. Intern Med 2009;48:49-55.
31. Metsvaht T, Ilmoja ML, Parm U, et al. Comparison of ampicillin plus gentamicin vs penicillin plus gentamicin in empiric treatment of neonates at risk of early onset sepsis. Acta Paediatr 2010;99:665-72.
32. Vick-Fragoso R, Hernández-Oliva G, Cruz-Alcázar J, et al. Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections. Infection 2009;37:407-17.
33. Chaudhuri A, Martinez-Martin P, Kennedy PG, Andrew Seaton R, Portegies P, Bojar M, Steiner I; EFNS Task Force. EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. Eur J Neurol 2008;15:649-59.
34. Tunkel AR, Hartman BJ, Kaplan SL, et al. Infectious Diseases Society of America. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267-84.
35. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005 Nov 15;41(10):1373-406.
36. Chey W, Wong B. American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection. Am J Gastroenterol 2007; 102:1808-1825.
37. Hunt R, Fallone C, Veldhuyzan van Zanten S, Sherman P, et al., CHSG 2004 participants. Canadian Helicobacter Study Group Consensus Conference: Update on the management of Helicobacter pylori--an evidence-based evaluation of six topics relevant to clinical outcomes in patients evaluated for H pylori infection. Can J Gastroenterol. 2004; 18(9):547-554.
38. Malfertheiner P, Megraud F, O'Morain C., et al. Current Concepts in the Management of Helicobacter pylori Infection. The Maastricht 2-2000 Consensus Report. European Helicobacter Pylori Study Group. Aliment Pharmacol Ther 2002; 16:167-180.
39. Veldhuyzen van Zanten SJ, Flook N, Chiba N, Armstrong D, An evidence-based approach to the management of uninvestigated dyspepsia in the era of Helicobacter pylori. Canadian Dyspepsia Working Group. CMAJ. 2000; 162(suppl 12):S3-23.
40. Bonow R, Carabello B, Chatterjee K et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e1-142.
41. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1-110.
42. Rosenfeld R, Andes D, Bhattacharyya N, et al. American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF). Clinical practice guideline: adult sinusitis. Otolaryngol Head Neck Surg 2007;137(Suppl 3):S1-31.
43. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 91: Treatment of urinary tract infections in nonpregnant women. Obstet Gynecol 2008;111:785-94.
44. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20.
45. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatr. 2004 May;113(5):1451-65.
46. Slavin R, Spector S, Bernstein IL, et al; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol. 2005;116(6):S13-S47.
47. American Academy of Pediatrics subcommittee on the management of sinusitis and committee on quality improvement. Clinical practice guideline: management of sinusitis. Pediatrics. 2001;108(3):798-808.
48. Bisno A, Gerber M, Gwaltney J, et al. Practice guideline for the diagnosis and management of group A Streptococcal pharyngitis. Clin Infect Dis. 2002;35(2):113-25.

49. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-S72.
50. Ramsdell J, Narsavage GL, Fink JB; American College of Chest Physicians' Home Care Network Working Group. Management of community-acquired pneumonia in the home: an American College of Chest Physicians clinical position statement. Chest. 2005 May;127(5):1752-63.
51. Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, et al; Working Group on Civilian Biodefense. Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA 2002;287(17):2236-52.
52. Bossi P, Tegnell A, Baka A, Van Loock F, et al.; Task Force on Biological and Chemical Agent Threats, Public Health Directorate, European Commission, Luxembourg. Bichat guidelines for the clinical management of anthrax and bioterrorism-related anthrax. Euro Surveill. 2004;9(12):1-7.
53. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. Circulation. Jun 2005;111:e394-e434.
54. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50:133-64.
55. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis. Clin Infect Dis. 2006;43:1089–134.
56. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2010. 117 p. Available at: www.goldcopd.com. Accessed October 2011.
57. Feder HM. Comparative tolerability of ampicillin, amoxicillin, and trimethoprim-sulfamethoxazole suspensions in children with otitis media. Antimicrob Agents Chemother.1982;21(3):426-7.
58. Stenstrom C, Lundgren K, Ingvarsson L, et al. Amoxycillin/clavulanate versus amoxycillin in recurrent otitis media and therapeutic failure in children. Acta Otolaryngol. 1991;111(1):120-9.
59. Thomsen J, Sederberg-Olsen J, Balle V, et al. Antibiotic treatment of children with secretory otitis media. Amoxicillin-clavulanate is superior to penicillin V in a double-blind randomized study. Arch Otolaryngol Head Neck Surg. 1997;123(7):695-9.
60. Chan KH, Mandel EM, Rockette HE, et al. A comparative study of amoxicillin-clavulanate and amoxicillin. Treatment of otitis media with effusion. Arch Otolaryngol Head Neck Surg. 1988;114(2):142-6.
61. Feder HM, Gerber MA, Randolph MF, et al. Once-daily therapy for streptococcal pharyngitis with amoxicillin. Pediatr. 1999;103:47-51.
62. Cohen R, Levy C, Doit C, et al. Six-day amoxicillin vs ten-day penicillin V therapy for group A streptococcal tonsillopharyngitis. Pediatr Infect Dis J. 1996;15(8):678-82.
63. Peyramond D, Portier H, Geslin P, et al. 6-day amoxicillin versus 10-day penicillin V for group A beta-haemolytic streptococcal acute tonsillitis in adults: a French multicentre, open-label, randomized study. Scand J Infect Dis. 1996;28(5):497-501.
64. Syrogiannopoulos GA, Bozdogan B, Grivea IN, et al. Two dosages of clarithromycin for five days, amoxicillin/clavulanate for five days or penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. Pediatr Infect Dis J. 2004;23(9):857-65.
65. Gopichand I, Williams GD, Medendorp SV, et al. Randomized, single-blinded comparative study of the efficacy of amoxicillin (40 mg/kg/day) versus standard-dose penicillin V in the treatment of group A streptococcal pharyngitis in children. Clin Pediatr. 1998;37(6):341-6.
66. Brook I. Treatment of patients with acute recurrent tonsillitis due to group A beta-haemolytic streptococci: a prospective randomized study comparing penicillin and amoxycillin/clavulanate potassium. J Antimicrob Chemother. 1989;24(2):227-33.
67. Curtin-Wirt C, Casey JR, Murray PC, et al. Efficacy of penicillin vs amoxicillin in children with group A beta hemolytic streptococcal tonsillopharyngitis. Clin Pediatr. 2003;42:219-25.
68. Dagan R, Bar-David Y. Comparison of amoxicillin and clavulanic acid (Augmentin) for the treatment of nonbullous impetigo. Am J Dis Child. 1989;143(8):916-8.
69. Stevens DL, Smith LG, Bruss JB, et al. Randomized comparison of linezolid (PNU-100766) versus oxacillin-dicloxacillin for treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother. 2000;44(12):3408-13.

70. Brathwaite AR. Double-blind trial of amoxycillin and ampicillin plus probenecid in the treatment of gonorrhoea in men. Br J Vener Dis. 1979;55(5):340-2.
71. Karney WW, Turck M, Holmes KK. Comparative therapeutic and pharmacological evaluation of amoxicillin and ampicillin plus probenecid for the treatment of gonorrhea. Antimicrob Ag Chemother. 1974;5(2):114-8.
72. Felman YM, William DC, Corsaro MC, et al. Comparison of ampicillin plus probenecid with amoxicillin plus probenecid for treatment of uncomplicated gonorrhea. Sex Transm Dis. 1979;6(2):72-4.
73. Latif AS, Sithole J, Bvumbe S, et al. Treating gonococcal urethritis in men: oral amoxycillin potentiated by clavulanate compared with intramuscular procaine penicillin. Br J Vener Dis. 1984;60(1):29-30.
74. Landis SJ, Ramphal R, Mansheim BJ, et al. Comparative efficacy of piperacillin and penicillin G in treatment of gonococcal urethritis. Antimicrob Ag Chemother. 1981;20(5):693-5.
75. Hook EW, Martin DH, Stephens J, Smith BS, Smith K. A randomized, comparative pilot study of azithromycin versus benzathine penicillin G for treatment of early syphilis. Sex Transm Dis. 2002;29(8):486-90.
76. Gallacher G, Erwin L, Scott PJ, et al. Augmentin (amoxycillin-clavulanic acid) compared with amoxycillin alone in the treatment of urinary tract infections in the elderly. J Infect. 1986;12(3):229-33.
77. Jibril HB, Ifere OA, Odumah DU, et al. An open, comparative evaluation of amoxycillin and amoxycillin plus clavulanic acid (Augmentin) in the treatment of bacterial pneumonia in children. Curr Med Res Opin. 1989;11(9):585-92.
78. Bansal A, Singhi SC, Jayashree M. Penicillin and gentamicin therapy vs amoxicillin/clavulanate in severe hypoxemic pneumonia. Indian J Pediatr. 2006;73:305-9.
79. Gaillat J, Bru JP, Sedallian A. Penicillin G/ofloxacin versus erythromycin/amoxicillin-clavulanate in the treatment of severe community-acquired pneumonia. Eur J Clin Microbiol Infect Dis. 1994;13(8):639-44.
80. Addo-Yobo E, Chisaka N, Hassan M, et al. Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study. Lancet. 2004;364:1141-8.
81. Jensen T, Pedersen SS, Stafanger G, et al. Comparison of amoxycillin/clavulanate with amoxycillin in children and adults with chronic obstructive pulmonary disease and infection with Haemophilus influenzae. Scand J Infect Dis. 1988;20(5):517-24.
82. Mackay AD. Amoxycillin versus ampicillin in treatment of exacerbations of chronic bronchitis. Br J Dis Chest. 1980;74(4):379-84.
83. Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med. 1996;101(1):68-76.
84. Gentry CA, Rodvold KA, Novak RM, Hershow RC, Naderer OJ. Retrospective evaluation of therapies for Staphylococcus aureus endocarditis. Pharmacotherapy. 1997;17(5):990-7.
85. Fernandez H, Claquin C, Guibert M, et al. Suspected postpartum endometritis: a controlled clinical trial of single-agent antibiotic therapy with Amox-CA (Augmentin) vs ampicillin-metronidazole +/- aminoglycoside. Eur J Obstet Gynecol Reprod Biol. 1990;36:60-74.
86. Cirau-Vigneron N, Barrier J, Becue J, et al. Amoxycillin/clavulanic acid (Augmentin) compared with a combination of aminopenicillin, aminoglycoside and metronidazole in the treatment of pelvic inflammatory disease. Pharmatherapeutica. 1989;5(5):312-9.
87. Resnik E, Harger JH, Kuller JA. Early postpartum endometritis. Randomized comparison of ampicillin/sulbactam vs ampicillin, gentamicin and clindamycin. J Reprod Med. 1994;39(6):467-72.
88. Spinnato JA, Youkilis B, Cook VD, et al. Antibiotic prophylaxis at Cesarean delivery. J Matern Fetal Med. 2000;9(6):348-50.
89. Kacmar J, Cheh E, Montagno A, Peipert JF. A randomized trial of azithromycin versus amoxicillin for the treatment of Chlamydia trachomatis in pregnancy. Infect Dis Obstet Gynecol. 2001;9(4):197-202.
90. Harkless L, Boghossian J, Pollak R, et al. An open-label, randomized study comparing efficacy and safety of intravenous piperacillin/tazobactam and ampicillin/sulbactam for infected diabetic foot ulcers. Surg Infect. 2005;6(1):27-40.
91. Tan JS, Wishnow RM, Talan DA, et al. Treatment of hospitalized patients with complicated skin and skin structure infections: double-blind, randomized multicenter study of piperacillin-tazobactam versus ticarcillin-clavulanate. Antimicrob Agents Chemother. 1993;37(8):1580-6.
92. Clay PG, Graham MR, Lindsey CC, et al. Clinical efficacy, tolerability, and cost savings associated with the use of open-label metronidazole plus ceftriaxone once daily compared with ticarcillin/clavulanate every 6 hours as empiric treatment for diabetic lower-extremity infections in older males [abstract]. Am J Geriatr Pharmacother. 2004;2(3):181.

93. Azimi PH, Barson WJ, Janner D, Swanson R, UNASYN Pediatric Study Group. Efficacy and safety of ampicillin/sulbactam and cefuroxime in the treatment of serious skin and skin structure infections in pediatric patients. Pediatr Infect Dis J. 1999 Jul;18(7):609-13.
94. Garau J, Twynholm M, Garcia-Mendez E, et al. Oral pharmacokinetically enhanced co-amoxiclav 2000/125 mg, twice daily compared with co-amoxiclav 875/125 mg, three times daily, in the treatment of community-acquired pneumonia in European adults. J Antimicrob Chemother. 2003;52(5):826-36.
95. File TM, Lode H, Kurz H, et al. Double-blind, randomized study of the efficacy and safety of oral pharmacokinetically enhanced amoxicillin-clavulanate (2,000/125 milligrams) versus those of amoxicillin-clavulanate (875/125 milligrams), both given twice daily for 7 days, in treatment of bacterial community-acquired pneumonia in adults. Antimicrob Agents Chemother. 2004;48(9):3323-31.
96. Allewelt M, Schuler P, Bolcskei PL, Mauch H, Lode H, Study Group on Aspiration Pneumonia. Ampicillin + sulbactam vs clindamycin ± cephalosporin for the treatment of aspiration pneumonia and primary lung abscess. Clin Microbiol Infect. 2004;10(2):163-70.
97. Joshi M, Bernstein J, Solomkin J, Wester BA, Kuye O, Piperacillin/tazobactam Nosocomial Pneumonia Study Group. Piperacillin/tazobactam plus tobramycin versus ceftazidime plus tobramycin for the treatment of patients with nosocomial lower respiratory tract infection. J Antimicrob Chemother. 1999;43(3):389-97.
98. Brun-Buisson C, Sollet JP, Schweich H, Briere S, Petit C, VAP Study Group. Treatment of ventilator-associated pneumonia with piperacillin-tazobactam/amikacin versus ceftazidime/amikacin: a multicenter randomized controlled trial. Clin Infect Dis. 1998;26(2):346-54.
99. Cohn SM, Lipsett PA, Buchman TG, et al. Comparison of intravenous/oral ciprofloxacin plus metronidazole versus piperacillin/tazobactam in the treatment of complicated intraabdominal infections. Ann Surg. 2000;232(2):254-62.
100. Polk HC, Fink MP, Laverdiere M, et al. Prospective randomized study of piperacillin/tazobactam therapy of surgically treated intra-abdominal infection. Amer Surgeon. 1993;59:598-605.
101. McKinnon PS, Neuhauser MM. Efficacy and cost of ampicillin-sulbactam and ticarcillin-clavulanate in the treatment of hospitalized patients with bacterial infections. Pharmacotherapy. 1999;19(6):724-33.
102. Fang H, Jiatai L, Lei G, et al. A randomized controlled clinical trial on piperacillin/tazobactam versus ticarcillin/clavulanic acid for the treatment of bacterial infections. Chin Med J. 1998;111(11):1039-43.
103. Rossini F, Terruzzi E, Verga L, et al. A randomized clinical trial of ceftriaxone and amikacin versus piperacillin tazobactam and amikacin in febrile patients with hematological neoplasia and severe neutropenia. Support Care Cancer. 2005;13:387-92.
104. Innes HE, Smith DB, O'Reilly SM, et al. Oral antibiotics with early hospital discharge compared with in-patient intravenous antibiotics for low-risk febrile neutropenia in patients with cancer: a prospective randomized controlled single centre study. Br J Cancer. 2003;89(1):43-9.
105. Petrilli AS, Cypriano M, Dantas LS, et al. Evaluation of ticarcillin/clavulanic acid versus ceftriaxone plus amikacin for fever and neutropenia in pediatric patients with leukemia and lymphoma. Braz J Infect Dis. 2003;7(2):111-20.
106. Philpott-Howard J, Burroughs A, Fisher N, et al. Piperacillin-tazobactam versus ciprofloxacin plus amoxicillin in the treatment of infective episodes after liver transplantation. J Antimicrob Chemother. 2003;52(6):993-1000.
107. File TM, Tan JS, Salstrom S, et al. Timentin versus piperacillin in the therapy of serious urinary tract infections. Amer J Med. 1985;79(suppl 5B):91-5.
108. Thanaviratananich S, Laopaiboon M, Vatanasapt P. Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD004975.
109. Lennon D, Farrell E, Martin D, et al. Once-daily amoxicillin versus twice-daily penicillin V in group A beta-haemolytic streptococcal pharyngitis. Arch Dis Child 2008;93:474-8.
110. Hazir T, Fox L, Nisar Y, et al. Ambulatory short-course high-dose oral amoxicillin for treatment of severe pneumonia in children: a randomised equivalency trial. Lancet. 2008 Jan 5;371(9606):49-56.
111. Atkinson M, Lakhanpaul M, Smyth A, et al. Comparison of oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children (PIVOT trial): a multicentre pragmatic randomised controlled equivalence trial. Thorax. 2007 Dec;62(12):1102-6.
112. Siempos I, Dimopoulos G, Korbila I, et al. Macrolides, quinolones and amoxicillin/clavulanate for chronic bronchitis: a meta-analysis. Eur Respir J. 2007 Jun;29(6):1127-37.
113. Kobayashi R, Sato T, Nakajima M, et al. Piperacillin/tazobactam plus ceftazidime versus sulbactam/ampicillin plus aztreonam as empirical therapy for fever in severely neutropenic pediatric patients. J Pediatr Hematol Oncol. 2009 Apr;31(4):270-3.

114. Bai Z, Yang K, Liu Y, et al. Azithromycin vs benzathine penicillin G for early syphilis: a meta-analysis of randomized clinical trials. Int J STD AIDS. 2008 Apr;19(4):217-21.
115. American Thoracic Society and the Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388–416.
116. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Eur Heart J 2009;30:2369-413.
117. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, LeFrock JL, Lew DP, Mader JT, Norden C, Tan JS; Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004 Oct 1;39(7):885-910.
118. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011;53:e25-76.
119. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52:1-38.
120. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM, Whitley RJ, Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303-27.

Alabama Medicaid Agency
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Pharmacotherapy Review of Quinolones
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I. Overview

The quinolones are approved to treat a variety of infections, including dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-11] They are broad-spectrum agents that directly inhibit bacterial DNA synthesis by blocking the actions of DNA gyrase and topoisomerase IV, which leads to bacterial cell death.[12-13]

The quinolones are most active against gram-negative bacilli and gram-negative cocci.[13] Ciprofloxacin has the most potent activity against gram-negative bacteria. Levofloxacin and moxifloxacin have greater potency against gram-positive cocci, and moxifloxacin has enhanced activity against anaerobic bacteria.[12-13] Gemifloxacin, levofloxacin and moxifloxacin are considered respiratory fluoroquinolones. They possess enhanced activity against *Streptococcus pneumoniae* while maintaining efficacy against *Hemophilus influenzae, Moraxella catarrhalis* and atypical pathogens. Resistance to the quinolones is increasing and cross-resistance among the various agents has been documented. Two mechanisms of bacterial resistance have been identified. These include mutations in chromosomal genes (DNA gyrase and/or topoisomerase IV) and altered drug permeability across the bacterial cell membranes.[12-13]

The quinolones that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Ciprofloxacin, levofloxacin and ofloxacin are available in a generic formulation. This class was last reviewed in August 2009.

Table 1. Quinolones Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ciprofloxacin	injection, extended-release tablet, suspension, tablet	Cipro®*, Cipro IV®*, Cipro XR®*, Proquin XR®	ciprofloxacin, ciprofloxacin ER
Gemifloxacin	tablet	Factive®	none
Levofloxacin	injection, solution, tablet	Levaquin®*	levofloxacin
Moxifloxacin	injection, tablet	Avelox®, Avelox ABC Pack®, Avelox IV®	none
Norfloxacin	tablet	Noroxin®	none
Ofloxacin	tablet	N/A	ofloxacin

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

The quinolones have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the quinolones that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Quinolones[1-11]

Organism	Ciprofloxacin	Gemifloxacin	Levofloxacin	Moxifloxacin	Norfloxacin	Ofloxacin
Gram-Positive Aerobes						
Bacillus anthracis	✔		✔			
Enterococcus faecalis	✔		✔	✔	✔	
Staphylococcus aureus	✔		✔	✔	✔	✔
Staphylococcus epidermidis	✔		✔		✔	
Staphylococcus saprophyticus	✔		✔		✔	
Streptococcus agalactiae					✔	
Streptococcus anginosus				✔		
Streptococcus constellatus				✔		
Streptococcus pneumoniae	✔	✔	✔	✔		✔
Streptococcus pyogenes	✔		✔	✔		✔
Gram-Negative Aerobes						
Campylobacter jejuni	✔					
Citrobacter diversus	✔					✔
Citrobacter freundii	✔				✔	
Enterobacter aerogenes					✔	✔
Enterobacter cloacae	✔		✔	✔	✔	
Escherichia coli	✔		✔	✔	✔	✔
Haemophilus influenzae	✔	✔	✔	✔		✔
Haemophilus parainfluenzae	✔	✔	✔	✔		
Klebsiella pneumoniae	✔	✔	✔	✔	✔	✔
Legionella pneumophila			✔			
Moraxella catarrhalis	✔	✔	✔	✔		
Morganella morganii	✔					
Neisseria gonorrhoeae	✔				✔	✔
Proteus mirabilis	✔		✔	✔	✔	✔
Proteus vulgaris	✔				✔	
Providencia rettgeri	✔					
Providencia stuartii	✔					
Pseudomonas aeruginosa	✔		✔		✔	✔
Salmonella typhi	✔					
Serratia marcescens	✔		✔		✔	
Shigella boydii	✔					
Shigella dysenteriae	✔					
Shigella flexneri	✔					
Shigella sonnei	✔					
Anaerobes						

Organism	Ciprofloxacin	Gemifloxacin	Levofloxacin	Moxifloxacin	Norfloxacin	Ofloxacin
Bacteroides fragilis				✔		
Bacteroides thetaiotaomicron				✔		
Clostridium perfringens				✔		
Peptostreptoococcus species				✔		
Miscellaneous Organisms						
Chlamydia pneumoniae		✔	✔	✔		
Chlamydia trachomatis						✔
Mycoplasma pneumoniae		✔	✔	✔		

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the quinolones are summarized in Table 3.

Table 3. Treatment Guidelines Using the Quinolones

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Guidelines on the Prevention, Diagnosis, and Treatment of Infective Endocarditis[61] (2009)**	• Antibiotic treatment of infective endocarditis due to oral streptococci and group D streptococci: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin or ceftriaxone for 4 weeks ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for 2 weeks ▪ Vancomycin for 4 weeks (in beta-lactam allergic patients) o Penicillin-resistant strains: ▪ Penicillin G or amoxicillin for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks plus gentamicin for 2 weeks (in beta-lactam allergic patients) • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for 4 to 6 weeks plus gentamicin for 3 to 5 days ▪ Vancomycin for 4 to 6 weeks plus gentamicin for 3 to 5 days (penicillin-allergic patients or methicillin-resistant staphylococci) o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks ▪ Vancomycin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks (penicillin-allergic patients or methicillin-resistant staphylococci) • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains ▪ Amoxicillin plus gentamicin for 4 to 6 weeks ▪ Ampicillin plus gentamicin for 4 to 6 weeks ▪ Vancomycin plus gentamicin for 6 weeks • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months ▪ Doxycycline plus quinolone for >18 months o *Bartonella* species: ▪ Ceftriaxone or ampicillin IV ▪ Doxycycline orally for 6 weeks plus gentamicin or netilmicin for 3 weeks o *Legionella* species: ▪ Erythromycin IV for 2 weeks, then orally for 4 weeks plus rifampin or ciprofloxacin orally for 6 weeks

Clinical Guideline	Recommendation(s)
	o *Mycoplasma* species: ▪ Newer fluoroquinolones for >6 months o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Penicillin G or streptomycin IV for 2 weeks, then cotrimoxazole orally for 1 year ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis (before or without pathogen identification): o Native valves: ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks o Prosthetic valves (early, <12 months post surgery) ▪ Vancomycin IV for 6 weeks, gentamicin IV for 2 weeks, and rifampin orally for 2 weeks o Prosthetic valves (late, ≥12 months post surgery) ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks
American College of Cardiology (ACC)/American Heart Association (AHA): **2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease[62] (2008)**	<u>Endocarditis Prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with CHD o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30-60 minutes before procedure): o Oral: amoxicillin o Unable to take oral medications: Ampicillin, cefazolin or ceftriaxone o Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis* o Penicillin G or ceftriaxone for 4 weeks o Ceftriaxone plus gentamicin for 2 weeks o Vancomycin for 4 weeks in patients allergic to penicillin • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin o Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2

Clinical Guideline	Recommendation(s)
	weeks o Vancomycin for 4 weeks in patients allergic to penicillin • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin o Ampicillin for 4 to 6 weeks or penicillin G plus gentamicin for 4 to 6 weeks o Vancomycin plus gentamicin for 6 weeks in patients allergic to penicillin • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials o Oxacillin-susceptible strains ▪ Nafcillin or oxacillin for 6 weeks plus the optional addition of gentamicin for 3 to 5 days ▪ Cefazolin for 6 weeks with the optional addition of gentamicin in patients allergic to penicillin o Oxacillin-resistant strains ▪ Vancomycin for 6 weeks o Oxacillin-resistant strains • Therapy for prosthetic valve endocarditis caused by staphylococci o Oxacillin-susceptible strains ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks o Oxacillin-resistant strains ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks • Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms o Ceftriaxone for 4 weeks o Ampicillin-sulbactam for 4 weeks o Ciprofloxacin for 4 weeks • Therapy for culture-negative endocarditis including *Bartonella* endocarditis o Native valve ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for 4 to 6 weeks o Prosthetic valve (early; ≤1 year) ▪ Vancomycin for 6 weeks, plus gentamicin for 2 weeks, plus cefepime for 6 weeks, plus rifampin for 6 weeks o Prosthetic valve (late; >1 year) ▪ Suspected *Bartonella*, culture negative • Ceftriaxone for 6 weeks plus gentamicin with/without doxycycline for 6 weeks ▪ Documented *Bartonella*, culture positive • Doxycycline for 6 weeks plus gentamicin for 2 weeks
American Heart Association (AHA): **Infective Endocarditis: Diagnosis, Antimicrobial Therapy, and Management of Complications**[85] **(2005)**	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus bovis*: o Penicillin-susceptible strains ▪ Penicillin G or ceftriaxone for 4 weeks ▪ Penicillin G or ceftriaxone plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Penicillin-resistant strains:

Clinical Guideline	Recommendation(s)
	▪ Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus bovis*: o Penicillin-susceptible strains ▪ Penicillin G or ceftriaxone for 6 weeks with or without gentamicin for 2 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Penicillin-resistant strains: ▪ Penicillin G or ceftriaxone for 6 weeks plus gentamicin for 6 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for 6 weeks with the option of adding gentamicin for 3-5 days ▪ For penicillin-allergic individuals: cefazolin for 6 weeks with the option of adding gentamicin for 3-5 days o Oxacillin-resistant strains ▪ Vancomycin for 6 weeks • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) o Oxacillin-resistant strains ▪ Vancomycin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) • Therapy for native valve or prosthetic valve enterococcal endocarditis o Strains susceptible to penicillin, gentamicin, and vancomycin: ▪ Ampicillin or penicillin G plus gentamicin for 4-6 weeks ▪ Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Strains susceptible to penicillin, streptomycin, and vancomycin and resistant to gentamicin: ▪ Ampicillin or penicillin G plus streptomycin for 4-6 weeks ▪ Vancomycin plus streptomycin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Strains resistant to penicillin and susceptible to aminoglycosides and vancomycin: ▪ β-lactamase–producing strain: • Ampicillin-sulbactam plus gentamicin for 6 weeks

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	• Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for 6 weeks o Strains resistant to penicillin, aminoglycosides and vancomycin: ▪ *E. faecium*: linezolid or quinupristin-dalfopristin for at least 8 weeks ▪ *E. faecalis*: imipenem/cilastatin plus ampicillin or ceftriaxone plus ampicillin for at least 8 weeks • Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin-sulbactam or ciprofloxacin for 4-6 weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin, gatifloxacin, or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin for 4-6 weeks ▪ Vancomycin plus gentamicin plus ciprofloxacin for 4-6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillins) o Prosthetic valve (early, <1 year): ▪ Vancomycin (for 6 weeks) plus gentamicin (for 2 weeks) plus cefepime (for 6 weeks) plus rifampin (for 6 weeks) o Prosthetic valve (late, ≥1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone (for 6 weeks) plus gentamicin (for 2 weeks) with or without doxycycline (for 6 weeks) ▪ Documented *Bartonella*, culture positive: • Doxycycline (for 6 weeks) plus gentamicin for (2 weeks)
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines: Management of Encephalitis[88] (2008)**	Empirical Therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or trimethoprim-sulfamethoxazole is recommended • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; trimethoprim-sulfamethoxazole is an alternative in the penicillin-

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	allergic patient • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered • *Tropheryma whipplei:* ceftriaxone, followed by either trimethoprim-sulfamethoxazole or cefixime, is recommended Rickettsioses and Ehrlichioses • *Anaplasma phagocytophilum:* doxycycline is recommended • *Ehrlichia chaffeensis:* doxycycline is recommended • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative Protozoa • *Acanthamoeba:* trimethoprim-sulfamethoxazole plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; trimethoprim-sulfamethoxazole alone and pyrimethamine plus either atovaquone, clarithromycin, azithromycin, or dapsone are alternatives • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended

European Federation of Neurological Societies (EFNS): **Guideline on the Management of Community-acquired Bacterial Meningitis[83] (2008)**	Empirical Therapy
	• Ceftriaxone 2 g every 12–24 hours or cefotaxime 2 g every 6–8 hours.
	• Alternative therapy: Meropenem 2 g every 8 hours or chloramphenicol 1 g every 6 hours.
	• If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg.
	• Ampicillin/Amoxicillin 2 g every 4 hours if *Listeria* is suspected.
	Pathogen Specific Therapy
	• Penicillin-sensitive pneumococcal meningitis:
	  o Benzyl penicillin 250,000 U/kg/day, ampicillin/amoxicillin 2 g every 4 hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every 6–8 hours
	  o Alternative therapy: meropenem 2 g every 8 hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily

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	• Pneumococcus with reduced susceptibility to penicillin or cephalosporins:
	  o Ceftriaxone or cefotaxime plus vancomycin ± rifampicin
	  o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin
	• Meningococcal meningitis:
	  o Benzyl penicillin, ceftriaxone, or cefotaxime
	  o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin
	• *Haemophilus influenzae* type B:
	  o Ceftriaxone or cefotaxime
	  o Alternative therapy: chloramphenicol–ampicillin/amoxicillin
	• Listerial meningitis:
	  o Ampicillin or amoxicillin 2 g every 4 hours ± gentamicin 1–2 mg every 8 hours for the first 7– 10 days
	  o Alternative therapy: trimethoprim–sulfamethoxazole 10–20 mg/kg every 6–12 hours or meropenem
	• *Staphylococcal* species:
	  o Flucloxacillin 2 g every 4 hours or vancomycin if penicillin allergy is suspected.
	  o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis.
	• Gram-negative *Enterobacteriaceae*:
	  o Ceftriaxone, cefotaxime or meropenem
	• Pseudomonal meningitis:
	  o Meropenem ± gentamicin

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Bacterial Meningitis[64] (2004)**	<u>Specific Therapy</u>
	• Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility.
	• *Streptococcus pneumoniae*
	  o Penicillin MIC ≥2 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime; alternative therapies include gatifloxacin or moxifloxacin
	  o Cefotaxime or ceftriaxone MIC ≥1.0 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime (consider addition of rifampin if MIC of ceftriaxone is >2 µg/mL); alternative therapies include gatifloxacin or moxifloxacin
	• *Neisseria meningitides*
	  o Penicillin MIC 0.1- 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include chloramphenicol, a fluoroquinolone or meropenem
	• *Escherichia coli* and other enterobacteriaceae
	  o Standard therapy includes a third-generation cephalosporin; alternative therapies include aztreonam, fluoroquinolone, meropenem, trimethoprim-sulfamethoxazole or ampicillin
	• *Pseudomonas aeruginosa*
	  o Standard therapies include cefepime or ceftazidime; alternative therapies include aztreonam, ciprofloxacin, or meropenem (addition of an aminoglycoside should be considered)
	• *Haemophilus influenzae* β-lactamase negative strains
	  o Standard therapy includes ampicillin; alternative therapies include ceftriaxone, cefotaxime, cefepime, chloramphenicol

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	or a fluoroquinolone
	• *Haemophilus influenzae* β-lactamase positive strains
	  o Standard therapy includes a third-generation cephalosporin; alternative therapies include cefepime, chloramphenicol or a fluoroquinolone
	• *Staphylococcus aureus* methicillin susceptible
	  o Standard therapy includes nafcillin or ofloxacin; alternative therapies include vancomycin or meropenem

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections[14] (2005)**	General Observations • Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first or second generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of methicillin-resistant S*taphylococcus aureus* (MRSA) strains. Animal Bites • Appropriate first-line therapy includes oral amoxicillin-clavulanate or penicillin VK plus dicloxacillin. Other options include fluoroquinolones, sulfamethoxazole-trimethoprim, and cefuroxime. The patient may also require an additional agent that is active against anaerobes, such as metronidazole or clindamycin. Animal Contact • Empirical treatment with the fluoroquinolones is recommended for anthrax associated with bioterrorism because of the potential for respiratory exposure. Route of administration is dependent on severity and degree of edema. • The recommended treatment of cat-scratch disease and bacillary angiomatosis is azithromycin. Alternatives include erythromycin, doxycycline, rifampin, sulfamethoxazole-trimethoprim and ciprofloxacin. • Erysipeloid may be associated with endocarditis; therefore high-dose penicillin is the treatment of choice. For cutaneous infection, penicillin or amoxicillin are appropriate, and cephalosporins, clindamycin and fluoroquinolones are effective alternatives. • Although no controlled trials for bubonic plague exist, streptomycin has been the drug of choice, although tetracycline and chloramphenicol are also considered to be appropriate therapy. Ciprofloxacin has been suggested as a drug for both treatment and prevention of plague due to biowarfare, despite lack of documented efficacy in humans. • Acutely ill patients with tularemia should be treated with streptomycin or gentamicin. In mild-moderate disease oral doxycycline or tetracycline is appropriate. Chloramphenicol and fluoroquinolones have also been used. Human Bites • Clenched-fist injuries typically require hospitalization and IV ampicillin-sulbactam, cefoxitin or one of the carbapenems. • Fluoroquinolones plus clindamycin or sulfamethoxazole-trimethoprim plus metronidazole can be used in patients with severe penicillin allergy. Necrotizing Infections • The combination of ampicillin-sulbactam, clindamycin and ciprofloxacin is first-line therapy for community-acquired mixed infection. The carbapenems or a combination of cefotaxime plus metronidazole or clindamycin, are also appropriate. • In cases of penicillin allergy, alternatives include clindamycin or metronidazole plus an aminoglycoside or fluoroquinolone.

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	Soft-tissue Infections Caused by Community-Acquired MRSA • They are often susceptible to non-β-lactam antibiotics, and standard treatment includes doxycycline, clindamycin, sulfamethoxazole-trimethoprim, rifampin, or fluoroquinolones (levofloxacin, gatifloxacin or moxifloxacin). Surgical Site Infections • For intestinal or genital tract surgical site infections, single agents such as cefoxitin, ceftizoxime, ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam, or carbapenems are indicated. • In cases where facultative and aerobic activity is desired, fluoroquinolones, third-generation cephalosporins, aztreonam, or aminoglycosides are recommended. • When anaerobic activity is desired, appropriate treatment includes clindamycin, metronidazole, chloramphenicol or a penicillin plus a β-lactamase inhibitor.
Infectious Diseases Society of America (IDSA): **Diagnosis and Treatment of Diabetic Foot Infections**[86] **(2004)**	• Empirical antibiotic regimens should be based on the clinical severity of the infection. • Current clinical data does not allow for the recommendation of any specific antibiotic regimen for diabetic foot infections (DFIs). • Suggested agents are derived from available published clinical trials and expert experience. • Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have US Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid is currently specifically approved for diabetic foot infections. • Suggested empirical antibiotic regimens for mild infections: dicloxacillin, clindamycin, cephalexin, trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, levofloxacin • Suggested empirical antibiotic regimens for moderate infections: trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, levofloxacin, cefoxitin, ceftriaxone, ampicillin/sulbactam, linezolid (with or without aztreonam), daptomycin (with or without aztreonam), ertapenem, cefuroxime (with or without metronidazole), ticarcillin/clavulanate, piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin • Suggested empirical antibiotic regimens for severe infections: piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin, imipenem-cilastatin, vancomycin and ceftazidime (with or without metronidazole)
World Gastroenterology Organization (WGO): **Acute Diarrhea**[90] **(2008)**	General Considerations • Antimicrobials are the drugs of choice for empirical treatment of traveler's diarrhea and of community-acquired secretory diarrhea when the pathogen is known. • Consider antimicrobial treatment for: o Persistent *Shigella*, *Salmonella*, *Campylobacter*, or parasitic infections o Infections in the aged, immunocompromised patients, and patients with impaired resistance, sepsis, or with prostheses o Moderate/severe traveler's diarrhea or diarrhea with fever and/or with bloody stools (quinolones as initial therapy or co-trimoxazole as a second choice)

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	• Nitazoxanide may be appropriate for *Cryptosporidium* and other infections, including some bacteria.
	• Rifaximin may also be useful.
	Antimicrobial Agents for the Treatment of Specific Causes of Diarrhea
	• Cholera
	  o First-line: doxycycline or tetracycline
	  o Alternative: azithromycin or ciprofloxacin
	• Shigellosis
	  o First-line: ciprofloxacin
	  o Alternative: pivmecillinam or ceftriaxone
	• Amebiasis
	  o First-line: metronidazole
	• Giardiasis
	  o First-line: metronidazole
	• *Campylobacter*
	  o First-line: azithromycin

Infectious Diseases Society of America (IDSA): **The Practice of Travel Medicine[63] (2006)**	Chemoprophylaxis • Bismuth subsalicylate–containing formulations and antibiotics have been proven effective in preventing traveler's diarrhea. • Probiotics, such as lactobacillus, have not demonstrated sufficient efficacy to be recommended. • Widespread drug resistance renders doxycycline and trimethoprim-sulfamethoxazole (TMP-SMX) no longer useful for prevention of traveler's diarrhea. • Chemoprophylaxis can contribute to development of resistant enteric bacteria and potentially predispose the traveler to infection with other deleterious pathogens, such as *Clostridium difficile.* • The routine use of antibiotic prophylaxis for travelers' diarrhea is not generally recommended. • Chemoprophylaxis may be considered in healthy travelers for whom staying well is critical and in special-needs travelers in whom the risk for diarrhea is increased or the consequences of a diarrheal episode may be severe. • When considering chemoprophylaxis, fluoroquinolone antibiotics remain the first choice. • Chemoprophylaxis should be recommended for no more than 2–3 weeks. Treatment • Fluid replacement and a diet restricted to liquids and bland foods may be appropriate, though they may not provide additional benefits beyond antibiotic treatment. • Symptomatic therapy with bismuth subsalicylate may be recommended in mild cases, but better agents exist for moderate-to-severe disease. • Loperamide has become the antimotility agent of choice. It is more efficacious in controlling diarrhea than bismuth subsalicylate and has an onset of action within the first 4 hours after ingestion. When it is used in combination with an antibiotic, there may be rapid improvement of traveler's diarrhea. • Antibiotics are effective in the treatment of traveler's diarrhea and can reduce the average duration of disease from several days to ~1 day. • Antibiotics that are recommended include fluoroquinolones, norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, azithromycin, and rifaximin. • Fluoroquinolones remain predictably active for empiric therapy in most parts of the world and remain the drugs of first choice.

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	• Antibiotics that are no longer recommended because of drug resistance worldwide are the sulfonamides, neomycin, ampicillin, doxycycline, tetracycline, trimethoprim alone, and TMP-SMX.
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Infectious Diarrhea[15] (2001)**	Recommendations for Therapy Against Specific Pathogens • *Shigella* species: o Trimethoprim-sulfamethoxazole (TMP-SMZ) o Fluoroquinolone o Nalidixic acid o Ceftriaxone o Azithromycin • *Salmonella,* non-typhi species: o Treatment is not routinely recommended; however, consider therapy in patients <6 months old or >50 years old, or patients that have a prosthesis, valvular heart disease, severe atherosclerosis, malignancy, or uremia. o TMP-SMZ o Fluoroquinolone • *Campylobacter* species o Erythromycin • *Escherichia coli* species o TMP-SMZ o Fluoroquinolone • *Aeromonas* or *Plesiomonas* species o TMP-SMZ o Fluoroquinolone • *Yersinia* species o Antibiotic therapy is not usually required. For severe infections or associated bacteremia, combination therapy with doxycycline, aminoglycosides TMP-SMZ or a fluoroquinolone is recommended. • *Vibrio cholerae* o Doxycycline or tetracycline o Fluoroquinolone • Toxigenic *Clostridium difficile* o Metronidazole • *Isospora* species o TMP-SMZ • *Cyclospora* species o TMP-SMZ
Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines[16] (2010)**	Chancroid • Recommended regimens: o Azithromycin 1 g orally in a single dose o Ceftriaxone 250 mg intramuscularly (IM) in a single dose o Ciprofloxacin 500 mg orally twice a day for 3 days o Erythromycin base 500 mg orally three times a day for 7 days Granuloma Inguinale (Donovanosis) • Recommended regimen: o Doxycycline 100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed • Alternative regimens: o Azithromycin 1 g orally once per week for at least 3 weeks and until all lesions have completely healed o Ciprofloxacin 750 mg orally twice a day for at least 3 weeks and until all lesions have completely healed o Erythromycin base 500 mg orally four times a day for at least

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	3 weeks and until all lesions have completely healed o Trimethoprim-sulfamethoxazole one double-strength (160 mg/800 mg) tablet orally twice a day for at least 3 weeks and until all lesions have completely healed • The addition of an aminoglycoside (e.g., gentamicin 1 mg/kg IV every 8 hours) to these regimens can be considered if improvement is not evident within the first few days of therapy. <u>Nongonococcal Urethritis</u> • Recommended regimens: o Azithromycin 1 g orally in a single dose o Doxycycline 100 mg orally twice a day for 7 days • Alternative regimens: o Erythromycin base 500 mg orally four times a day for 7 days o Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days o Levofloxacin 500 mg orally once daily for 7 days o Ofloxacin 300 mg orally twice a day for 7 days <u>Chlamydial Infections</u> • Recommended regimens: o Azithromycin 1 g orally in a single dose o Doxycycline 100 mg orally twice a day for 7 days • Alternative regimens: o Erythromycin base 500 mg orally four times a day for 7 days o Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days o Levofloxacin 500 mg orally once daily for 7 days o Ofloxacin 300 mg orally twice a day for 7 days <u>Epididymitis</u> • Recommended regimens : o Ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg orally twice a day for 10 days • For acute epididymitis most likely caused by enteric organisms: o Levofloxacin 500 mg orally once daily for 10 days o Ofloxacin 300 mg orally twice a day for 10 days
Infectious Diseases Society of America (IDSA)/European Society for Microbiology and Infectious Diseases (ESCMID): **International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women[18] (2010)**	<u>Acute Uncomplicated Bacterial Cystitis</u> • Nitrofurantoin monohydrate/macrocrystals (100 mg BID for 5 days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage. • Trimethoprim-sulfamethoxazole (160/800 mg BID for 3 days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible. • Fosfomycin (3 g in a single dose) is an appropriate choice for therapy where it's available due to minimal resistance and propensity for collateral damage, but it appears to be less effective compared to standard short-course regimens. • Ofloxacin, ciprofloxacin and levofloxacin are highly efficacious in 3-day regimens, but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis. • β-lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in 3-7 day regimens are appropriate choices for therapy when other recommended agents cannot be used. Other β-lactams, such as cephalexin are less well studied, but may also be

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	appropriate in certain settings. The β-lactams are generally less effective and have more adverse effects compared with other UTI antimicrobials. For these reasons, β-lactams should be used with caution for uncomplicated cystitis. • Amoxicillin or ampicillin should not be used for empirical treatment given the relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. <u>Acute Pyelonephritis</u> • Oral ciprofloxacin (500 mg BID) for 7 days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice when resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. A long-acting antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) may replace the initial one time IV ciprofloxacin, and is recommended if the fluoroquinolone resistance is thought to exceed 10%. • Once-daily fluoroquinolones (ciprofloxacin 100 mg extended-release for 7 days, levofloxacin 750 mg for 5 days) is an appropriate choice when resistance to community uropathogens is not known to exceed 10%. If resistance is thought to exceed 10%, an initial intravenous dose of long-acting parenteral antimicrobial (ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral trimethoprim/sulfamethoxazole (160/800 mg BID) for 14 days is an appropriate choice of therapy when the uropathogen is known to be susceptible. If susceptibility is unknown, an initial IV dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral β-lactams are less effective than other available agents for the treatment of pyelonephritis. If an oral β-lactam is used, an initial IV dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • For patients requiring hospitalization, initial treatment with an intravenous antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin with or without an aminoglycoside, or a carbapenem is recommended. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results.

American College of Obstetricians and Gynecologists (ACOG): **Treatment of Urinary Tract Infections in Nonpregnant Women**[17] **(2008)**	• For uncomplicated acute bacterial cystitis, recommended treatment regimens are as follows:
	  o Trimethoprim–sulfamethoxazole: 1 tablet (160 mg trimethoprim–800 mg sulfamethoxazole) twice daily for 3 days.
	  o Trimethoprim 100 mg twice daily for 3 days.
	  o Ciprofloxacin 250 mg twice daily for 3 days, levofloxacin 250 mg once daily for 3 days, norfloxacin 400 mg twice daily for 3 days, or gatifloxacin 200 mg, once daily for 3 days.
	  o Nitrofurantoin macrocrystals 50 to 100 mg 4 times daily for 7 days, or nitrofurantoin monohydrate 100 mg twice daily for 7 days.
	  o Fosfomycin tromethamine, 3-g dose (powder) single dose.

Working Group on Civilian Biodefense: **Anthrax as a Biological Weapon, Updated Recommendations for Management**[26] **(2002)**	<u>Inhalation Anthrax in the Contained Casualty Setting - Adults</u> • Ciprofloxacin 400 mg IV every 12 hours initially, then 500 mg by mouth twice daily when clinically appropriate OR • Doxycycline 100 mg IV every 12 hours initially with either one or two of the following: rifampin, vancomycin, penicillin, ampicillin,

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	chloramphenicol, imipenem, clindamycin, and/or clarithromycin. Switch to 100 mg by mouth twice daily when clinically appropriate. Inhalation Anthrax in the Contained Casualty Setting - Children • Ciprofloxacin 10-15 mg/kg every 12 hours IV, then 10-15 mg/kg by mouth every 12 hours when clinically appropriate OR • Doxycycline (if ≤45 kg–2.2 mg/kg IV; if >45 kg–100 mg IV) every 12 hours initially with either one or two of the following: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and/or clarithromycin. Switch to oral therapy when clinically appropriate using same IV dose. Inhalation Anthrax in a Mass Casualty Setting - Adults • Recommended treatment: ciprofloxacin 500 mg by mouth every 12 hours • Alternative treatment option: doxycycline 100 mg by mouth every 12 hours or amoxicillin 500 mg by mouth every 8 hours Inhalation Anthrax in a Mass Casualty Setting - Children • Recommended treatment: ciprofloxacin 10-15 mg/kg by mouth every 12 hours • Alternative treatment option: amoxicillin 500 mg by mouth every 8 hours (weight ≥20 kg) or amoxicillin 40 mg/kg by mouth every 8 hours (weight <20 kg) Inhalation Anthrax in a Mass Casualty Setting – Pregnant Women • Recommended treatment: ciprofloxacin 500 mg by mouth every 12 hours • Alternative treatment option: amoxicillin 500 mg by mouth every 8 hours Cutaneous Anthrax Infection Associated with a Bioterrorism Attack - Adults • Ciprofloxacin 500 mg by mouth every 12 hours OR • Doxycycline 100 mg by mouth every 12 hours Cutaneous Anthrax Infection Associated with a Bioterrorism Attack - Children • Ciprofloxacin 10-15 mg/kg by mouth every 12 hours OR • Doxycycline 2.2 mg/kg (weight ≤45 kg) or 100 mg (weight >45 kg) by mouth every 12 hours
American College of Chest Physicians (ACCP): **Chronic Cough Due to Acute Bronchitis, ACCP Evidence-Based Clinical Practice Guidelines[20] (2006)**	• For patients with the putative diagnosis of acute bronchitis, routine treatment with antibiotics is not justified and should not be offered.
American College of Chest Physicians (ACCP): **Chronic Cough Due to Chronic Bronchitis, ACCP Evidence-Based Clinical Practice Guidelines[19] (2006)**	• In stable patients with chronic bronchitis, there is no role for long-term prophylactic therapy with antibiotics. • In patients with acute exacerbations of chronic bronchitis, the use of antibiotics is recommended; patients with severe exacerbations and those with more severe airflow obstruction at baseline are the most likely to benefit.
Global Initiative for Chronic Obstructive Lung Disease (GOLD): **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[21]**	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in COPD. • There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful. • Based on current available evidence, antibiotics should be given to: o Patients with exacerbations of COPD with the following three

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(2010)	cardinal symptoms: dyspnea, sputum volume, and sputum purulence. o Patients with exacerbations of COPD with two of the cardinal symptoms, if the increased purulence of sputum is one of the two symptoms. o Patients with a severe exacerbation of COPD that requires mechanical ventilation (invasive or noninvasive). • Antibiotic treatment in exacerbations of COPD: o Group A (mild exacerbation; no risk factors for poor outcome) ▪ Recommended oral treatment: β-lactam (penicillin, ampicillin, amoxicillin), tetracycline, or trimethoprim-sulfamethoxazole ▪ Alternative oral treatment: β-lactam/β-lactamase inhibitor, macrolides, second or third generation cephalosporin, or ketolides o Group B (moderate exacerbation with risk factor(s) for poor outcome) ▪ Recommended oral treatment: β-lactam/β-lactamase inhibitor ▪ Alternative oral treatment: fluoroquinolones (gemifloxacin, levofloxacin, moxifloxacin) ▪ Parenteral treatment: β-lactam/β-lactamase inhibitor, second or third generation cephalosporin, or fluoroquinolones (levofloxacin, moxifloxacin) o Group C (severe exacerbation with risk factors for *P. aeruginosa* infection) ▪ Recommended oral treatment: fluoroquinolones (ciprofloxacin, levofloxacin) ▪ Parenteral treatment: fluoroquinolones (ciprofloxacin, levofloxacin) or β-lactam with *P. aeruginosa* activity
Infectious Diseases Society of America (IDSA): **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age**[24] **(2011)**	Outpatient Treatment • Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia (CAP), because viral pathogens are responsible for the great majority of clinical disease. • Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate CAP suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*. • For patients allergic to amoxicillin, the following agents are considered alternative treatment options: o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil) o Levofloxacin (oral therapy) o Linezolid (oral therapy) • Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with CAP caused by atypical pathogens. Inpatient Treatment • Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with CAP when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *S. pneumoniae*. • Empiric therapy with a third-generation parenteral cephalosporin

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	(ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. • Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *M. pneumoniae* and *C. pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *S. aureus*.

Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS): **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults[22] (2007)**	<u>Empirical Antimicrobial Therapy</u>
	• Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.
	• Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.
	• Outpatient treatment
	  o Previously healthy and no risk factors for drug-resistant *S. pneumoniae* (DRSP) infection:
	  ▪ Macrolide (azithromycin, clarithromycin, or erythromycin)
	  ▪ Doxycycline
	  o Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected); or other risks for DRSP infection:
	  ▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin)
	  ▪ β-lactam plus a macrolide (High-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide.)
	  o In regions with a high rate of infection with high-level macrolide-resistant *S. pneumoniae,* consider the use of alternative agents listed above for any patient, including those without comorbidities.
	• Inpatient, non-ICU treatment
	  o Respiratory fluoroquinolone
	  o β-lactam plus a macrolide (Preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients).
	• Inpatient, ICU treatment
	  o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (for penicillin-

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	allergic patients, a respiratory fluoroquinolone and aztreonam are recommended.) o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam). o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.
American College of Chest Physicians (ACCP): **Management of Community-Acquired Pneumonia in the Home: An American College of Chest Physicians Clinical Position Statement[23]** **(2005)**	• Antibiotic choice and route of administration are central to an appropriate in-home treatment plan. The oral route is recommended if the patient can tolerate it, and if the availability and activity of the agent are adequate. • Although treatment is facilitated if the etiologic agent is known (pathogen-directed treatment for CAP is provided in the IDSA guidelines), most outpatient treatment is empiric. • The use of a macrolide, doxycycline, or fluoroquinolone agent, as recommended both by the IDSA and the ATS guidelines, may be appropriate empiric outpatient treatment for low-risk patients (i.e., otherwise young healthy individuals). Alternatives to these agents in low-risk patients are amoxicillin/clavulanate and some second-generation cephalosporins (e.g., cefuroxime, cefpodoxime, or cefprozil). • A lack of response to treatment with macrolides and fluoroquinolones has been reported. Some authorities prefer to reserve the use of fluoroquinolones for older patients, patients who are allergic or intolerant to macrolides, patients who have recently received macrolide treatment, patients with comorbidities, patients with documented infections with highly resistant pneumococci, or patients with a lack of response to treatment with another agent. • The IDSA and ATS recommendations generally agree that a patient who is at high risk either because of complicated comorbidities or extensive prior antibiotic use may be a candidate for treatment with either a β-lactam/macrolide combination or a antipneumococcal fluoroquinolone. • Double therapy with either a β-lactam/macrolide combination or a β-lactam/ antipneumococcal fluoroquinolone should be considered in patients who would normally be considered for ICU admission but have chosen to remain in the home.
American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA): **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia[60]** **(2005)**	• Select an initial empiric therapy based on the absence or presence of risk factors for multidrug-resistant (MDR) pathogens. These risk factors include prolonged duration of hospitalization (5 days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy. • Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins. • In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same

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	class of antibiotics.
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for MDR pathogens, early onset, and any disease severity:
	  o Ceftriaxone OR
	  o Levofloxacin, moxifloxacin, ciprofloxacin OR
	  o Ampicillin/sulbactam OR
	  o Ertapenem
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for MDR pathogens and all disease severity – combination antibiotic therapy is recommended as follows:
	  o Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if MRSA risk factors are present or there is a high incidence locally.

Infectious Diseases Society of America (IDSA): **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children[28] (2010)**	Community-Acquired Infection in Adults: Mild to Moderate Severity • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*E. Coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. Community-Acquired Infection in Adults: High Severity • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *E. coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E. coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent

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	effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended. • Use of agents effective against MRSA or yeast is not recommended in the absence of evidence of infection due to such organisms. <u>Community-Acquired Infection in Pediatric Patients:</u> • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected MRSA or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. <u>Health Care-Associated Infection:</u> • Therapy should be based on microbiologic results. To achieve empiric coverage, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. <u>Cholecystitis and Cholangitis:</u> • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.
Infectious Diseases Society of America (IDSA): **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus*[87] (2011)**	<u>Skin and Soft-Tissue Infections (SSTIs)</u> • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia),

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	associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired (CA) MRSA is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for CA-MRSA is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of CA-MRSA in outpatients with SSTI, oral antibiotic options include the following: clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and CA-MRSA is desired, options include the following: clindamycin alone or TMP-SMX or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of SSTIs is not recommended. • For hospitalized patients with complicated SSTIs, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for MRSA should be considered pending culture data. Options include the following: vancomycin intravenous (IV), linezolid oral (PO) or IV, daptomycin IV, telavancin IV, and clindamycin IV or PO. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to MRSA-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with cSSTIs, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin IV is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative. <u>MRSA Bacteremia and Infective Endocarditis (Native Valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin IV for at least 2 weeks is recommended. For complicated bacteremia, 4–6 weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, IV vancomycin or daptomycin for 6 weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>MRSA Bacteremia and Infective Endocarditis (Prosthetic Valve)</u> • IV vancomycin plus rifampin PO/IV for at least 6 weeks plus gentamicin IV for 2 weeks. • In children, vancomycin IV is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from 2 to 6 weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin IV may be an option. Clindamycin or

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	linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus.
	• Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis.
	<u>Management of MRSA Pneumonia</u>
	• For hospitalized patients with severe community-acquired pneumonia, empirical therapy for MRSA is recommended pending sputum and/or blood culture results.
	• For health care–associated MRSA (HA-MRSA) or CA-MRSA pneumonia, IV vancomycin or linezolid PO/IV or clindamycin PO/IV, if the strain is susceptible, is recommended for 7–21 days, depending on the extent of infection.
	• In children, IV vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin IV can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative.
	<u>Management of MRSA Bone and Joint Infections</u>
	• Antibiotics available for parenteral administration include IV vancomycin and daptomycin.
	• Some antibiotic options with parenteral and oral routes of administration include the following: TMP-SMX in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.
	• A minimum 8-week course is recommended. Some experts suggest an additional 1–3 months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with TMP-SMX, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities.
	• For septic arthritis, refer to antibiotic choices for osteomyelitis. A 3 to 4-week course of therapy is suggested.
	<u>Management of MRSA Infections of the CNS</u>
	• Meningitis
	  o IV vancomycin for 2 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid or TMP-SMX.
	  o For CNS shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid (CSF) cultures are repeatedly negative.
	• Brain abscess, subdural empyema, spinal epidural abscess
	  o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and TMP-SMX.
	• Septic thrombosis of cavernous or dural venous sinus
	  o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and TMP-SMX.
	  o IV vancomycin is recommended in children.

Infectious Diseases Society of America (IDSA): **Clinical Practice Guideline for the Use**	<u>Initial Antibiotic Therapy</u> • Oral route: o For low-risk adults only; use ciprofloxacin plus amoxicillin-

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of Antimicrobial Agents in Neutropenic Patients with Cancer[25] (2010)	clavulanate
	• Monotherapy with vancomycin not indicated:
	  o Choose therapy with 1 of the following agents: cefepime or ceftazidime, or imipenem or meropenem
	• Two drugs without vancomycin:
	  o Choose an aminoglycoside plus antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem
	• Vancomycin plus 1 or 2 antibiotics:
	  o Choose cefepime or ceftazidime plus vancomycin, with or without an aminoglycoside; carbapenem plus vancomycin, with or without an aminoglycoside; or antipseudomonal penicillin plus an aminoglycoside and vancomycin
	Modification of Therapy During the First Week of Treatment
	• Patient becomes afebrile in 3–5 days:
	  o Adjust therapy to the most appropriate drug(s). If no etiologic agent is identified and if the patient is at low risk initially, and oral antibiotic treatment was begun with no subsequent complications, continue use of the same drugs.
	  o If the patient was at low risk initially and therapy with intravenous drugs was begun with no subsequent complications, the regimen may be changed after 48 h to oral ciprofloxacin plus amoxicillin-clavulanate for adults or cefixime for children.
	  o If the patient is at high risk initially with no subsequent complications, continue use of the same intravenous drugs.
	• Persistent fever throughout the first 3–5 days:
	  o Reassess therapy on day 3. If there is no clinical worsening, continue use of the same antibiotics; stop vancomycin use if cultures do not yield organisms.
	  o If there is progressive disease, change antibiotics.
	  o If the patient is febrile after 5 days, consider adding an antifungal drug
	Antibiotic Prophylaxis for Afebrile Neutropenic Patients
	• Use of antibiotic prophylaxis is not routine because of emerging antibiotic resistance, except for the use of trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* pneumonitis.

Surgical Infection Prevention Guideline Writers Workgroup (SIPGWW): **Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project[89] (2004)**	General Considerations • There is published evidence to support the use of many prophylactic antimicrobial regimens besides those included in this advisory statement or in existing guidelines. • Factors such as cost, half-life, safety, and antimicrobial resistance favor the use of older agents with a relatively narrow spectrum. • The use of newer, broad-spectrum drugs that are front-line therapeutic agents should be avoided in surgical prophylaxis to reduce emergence of bacterial strains that are resistant to these antimicrobials. Gynecologic and Obstetrical Surgery • For abdominal or vaginal hysterectomy, cefotetan is preferred, but reasonable alternatives are cefazolin and cefoxitin. In cases of β-lactam allergy, the workgroup recommends the use of one of the following regimens: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; metronidazole combined with gentamicin or ciprofloxacin; or clindamycin monotherapy. A single 750-mg dose of levofloxacin can be substituted for ciprofloxacin. • For cesarean section, a narrow-spectrum antimicrobial regimen similar to that recommended for hysterectomy provides adequate prophylaxis.

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	Orthopedic Total Joint (Hip and Knee) Arthroplasty • The preferred antimicrobials for prophylaxis in patients undergoing hip or knee arthroplasty are cefazolin and cefuroxime. • Vancomycin or clindamycin may be used in patients with serious allergy or adverse reactions to β-lactams. Cardiothoracic and Vascular Surgery • The recommended antimicrobials for cardiothoracic and vascular operations include cefazolin or cefuroxime. • For patients with serious allergy or adverse reaction to b-lactams, vancomycin is appropriate, and clindamycin may be an acceptable alternative. Colorectal Surgery • Antimicrobial prophylaxis for colorectal operations can consist of an orally administered antimicrobial bowel preparation, a preoperative parenteral antimicrobial, or the combination of both. • Recommended oral prophylaxis consists of neomycin plus erythromycin or neomycin plus metronidazole, initiated no more than 18–24 h before the operation, along with administration of a mechanical bowel preparation. • Cefotetan or cefoxitin are recommended for parenteral prophylaxis, and the combination of parenteral cefazolin and metronidazole is also recommended as an alternative. • For patients with confirmed allergy or adverse reaction to β-lactams, use of one of the following regimens is recommended: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; or metronidazole combined with gentamicin or ciprofloxacin. A single 750-mg dose of levofloxacin can be substituted for ciprofloxacin.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the quinolones are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Quinolones[1-11]

Indication	Ciprofloxacin	Gemifloxacin	Levofloxacin	Moxifloxacin	Norfloxacin	Ofloxacin
Dermatological Infections						
Skin and skin-structure infections	✔ §*		✔	✔		✔
Gastrointestinal Infections						
Infectious diarrhea	✔ §					
Genitourinary Infections						
Cystitis	✔ §					✔
Pelvic inflammatory disease						✔
Prostatitis	✔ §*		✔		✔	✔
Pyelonephritis	✔ §†*		✔			
Urethritis/cervicitis (gonococcal)	✔ §				✔	✔
Urethritis/cervicitis (non-gonococcal)						✔
Urinary tract infections	✔ §†*		✔		✔	✔
Respiratory Infections						
Acute exacerbations of chronic bronchitis		✔	✔	✔		✔
Inhalation anthrax (post-exposure)	✔ §*		✔			
Pneumonia (community-acquired)		✔	✔	✔		✔
Pneumonia (nosocomial)	✔ *		✔			
Respiratory tract infections (lower)	✔ §*					
Sinusitis	✔ §*		✔	✔		
Miscellaneous Infections						
Bone and/or joint infections	✔ §*					
Empiric therapy for febrile neutropenic patients	✔ *					
Intra-abdominal infections	✔ §*			✔		
Typhoid fever	✔ §					

§Immediate-release formulation
†Extended-release formulation
*IV formulation

IV. Pharmacokinetics

The pharmacokinetic parameters of the quinolones are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Quinolones[1-11]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Ciprofloxacin	60-80	20-40	Liver	Renal (30-57) Feces (20-35)	IR: 3-6 ER: 6-7
Gemifloxacin	71	60-70	Liver	Renal (36) Feces (61)	4-12
Levofloxacin	99	24-38	Liver	Renal (87) Feces (4)	6-8
Moxifloxacin	90	30-50	Liver (52)	Renal (20) Feces(25)	8-16
Norfloxacin	30-40	10-15	Liver	Renal (30) Feces (30)	3-4
Ofloxacin	90-98	20-32	Liver	Renal (65-80) Feces (4-8)	5-7.5

ER=extended-release, IR=immediate-release

V. Drug Interactions

Significant drug interactions with the quinolones are listed in Table 6.

Table 6. Significant Drug Interactions with the Quinolones[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Quinolones (levofloxacin, moxifloxacin)	1	Arsenic	May cause additive QT interval prolongation.
Quinolones (levofloxacin, moxifloxacin)	1	Bepridil	May cause additive QT interval prolongation.
Quinolones (levofloxacin, moxifloxacin)	1	Butyrophenones	May cause additive QT interval prolongation.
Quinolones (levofloxacin)	1	Chloroquine	May cause additive QT interval prolongation.
Quinolones (levofloxacin, moxifloxacin)	1	Cisapride	The risk of cardiovascular side effects may be increased. The mechanism is unknown.
Quinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin)	1	Antiarrhythmic agents	Both quinolones and antiarrhythmics can cause prolongation of the QT interval. Additive prolongation may occur.
Quinolones (levofloxacin, moxifloxacin)	1	Halofantrine	May cause additive QT interval prolongation.
Quinolones (levofloxacin, moxifloxacin)	1	Macrolides and detolides	Pharmacologic effects of macrolides/ketolides and quinolones on the cardiac conduction system and QT

Generic Name(s)	Significance Level	Interaction	Mechanism
			interval may be additive.
Quinolones (levofloxacin, moxifloxacin)	1	Maprotiline	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin)	1	Methadone	Methadone inhibits cardiac potassium channels and prolongs QT interval. This may become significant with larger doses and in combination with other drugs that also prolong QT interval.
Quinolones (levofloxacin, moxifloxacin)	1	Nilotinib	May cause additive QT interval prolongation.
Quinolones (levofloxacin, moxifloxacin)	1	Phenothiazines	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased. The mechanism is unknown.
Quinolones (levofloxacin, moxifloxacin)	1	Pimozide	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, levofloxacin)	1	Sulfonylureas	The hypoglycemic effect of sulfonylureas may be increased. The mechanism is unknown.
Quinolones (levofloxacin, moxifloxacin)	1	Tacrolimus	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, norfloxacin)	1	Theophylline	Inhibition of hepatic metabolism of theophylline leads to increased theophylline levels and toxicity can occur.
Quinolones (ciprofloxacin)	1	Tizanidine	Quinolones may inhibit tizanidine metabolism (CYP1A2). Tizanidine plasma concentrations may be elevated, increasing the pharmacologic and adverse effects (e.g., dizziness, hypotension).
Quinolones (levofloxacin, moxifloxacin)	1	Toremifene	Pharmacologic effects of toremifene and quinolones on electrical conduction of the heart may be additive.
Quinolones (levofloxacin, moxifloxacin)	1	Vandetanib	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin)	1	Warfarin	The effect is an increased anticoagulant effect of warfarin. The mechanism is unknown.
Quinolones (levofloxacin, moxifloxacin)	1	Ziprasidone	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased. The mechanism is unknown.

Generic Name(s)	Significance Level	Interaction	Mechanism
Quinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin)	2	Aluminum Salts	Gastrointestinal (GI) absorption of quinolones may be decreased, resulting in decreased pharmacologic effects of quinolones. Reduced GI acidity may be an additional mechanism.
Quinolones (ciprofloxacin, norfloxacin)	2	Caffeine	Inhibition of hepatic microsomal enzymes by quinolones may decrease the metabolic elimination of caffeine.
Quinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin)	2	Calcium Salts	Gastrointestinal absorption of quinolones may be decreased, resulting in decreased pharmacologic effects of quinolones.
Quinolones (ciprofloxacin)	2	Clozapine	Inhibition of cytochrome P450 1A2 isoenzymes by ciprofloxacin may decrease the metabolic elimination of clozapine. This may increase clozapine blood levels, leading to increased risk of clozapine's adverse effects.
Quinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin)	2	Corticosteroids	Adverse effects may be additive or synergistic. Drug-induced tendon rupture may be increased by corticosteroid coadministration, especially in those 60 years of age or greater.
Quinolones (ciprofloxacin, gemifloxacin, norfloxacin)	2	Didanosine	The pharmacologic effects of quinolones may be decreased. The magnesium and aluminum cations in the buffers present in didanosine tablets decrease GI absorption of quinolones via chelation.
Quinolones (ciprofloxacin)	2	Duloxetine	Inhibition of cytochrome P450 1A2 by ciprofloxacin may decrease the metabolic elimination of duloxetine.
Quinolones (ciprofloxacin)	2	Hydantoins	Ciprofloxacin may decrease serum concentrations and pharmacologic effects of hydantoins, especially in elderly patients. The mechanism is unknown.
Quinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin,	2	Iron Salts	The formation of insoluble chelates with iron decreases gastrointestinal absorption of quinolones.

Generic Name(s)	Significance Level	Interaction	Mechanism
ofloxacin)			
Quinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin)	2	Ketorolac	Ketorolac may reduce the renal elimination of quinolones and increase the risk of central nervous system stimulation and seizures.
Quinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin)	2	Magnesium Salts	The gastrointestinal (GI) absorption of quinolones may be decreased due to formation of poorly soluble chelates with magnesium. Reduced GI acidity may be an additional mechanism.
Quinolones (ciprofloxacin)	2	Methotrexate	Displacement of methotrexate from protein binding sites by ciprofloxacin may increase plasma concentrations of methotrexate.
Quinolones (norfloxacin)	2	Mycophenolate	Changes in gut flora due to combination antimicrobial therapy with norfloxacin oral and metronidazole may decrease the enterohepatic recirculation of mycophenolate mofetil oral thereby decreasing mycophenolate exposure.
Quinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin)	2	NSAIDs	NSAIDs may reduce the renal elimination of quinolones and increase the risk of central nervous system stimulation and seizures.
Quinolones (ciprofloxacin)	2	Sevelamer	Decreased gastrointestinal absorption of ciprofloxacin is suspected.
Quinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin)	2	Sucralfate	The aluminum in sucralfate may complex with quinolones to decrease gastrointestinal absorption.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the quinolones are listed in Table 7. The boxed warning for the quinolones is listed in Table 8.

Table 7. Adverse Drug Events (%) Reported with the Quinolones[1-11]

Adverse Events	Ciprofloxacin	Gemifloxacin	Levofloxacin	Moxifloxacin	Norfloxacin	Ofloxacin
Cardiovascular						
Angina pectoris	<1	-	-	0.1-1	-	-
Atrial fibrillation	-	-	-	0.1-1	-	-
Atrial flutter	<1	-	-	-	-	-
Bradycardia	-	-	-	0.1-1	-	-
Cardiac arrest	<1	-	0.1-1	0.1-1	0.1-0.2	<1
Cerebral thrombosis	<1	-	-	-	-	-
Congestive heart failure	-	-	-	0.1-1	-	-
Hypertension	<1	-	-	0.1-1	-	<1
Hypotension	<1	-	-	0.1-1	-	<1
Myocardial infarction	<1	-	-	-	-	-
Palpitations	<1	-	0.1-1	0.1-1	0.1-0.2	<1
QT prolongation	✔	-	✔	0.1-1	✔	-
Supraventricular tachycardia	-	✔	-	-	-	-
Syncope	<1	✔	0.1-1	0.1-1	-	<1
Tachycardia	<1	-	✔	0.1-1	-	-
Ventricular arrhythmia	-	-	0.1-1	✔	✔	-
Ventricular ectopy	<1	-	-	-	-	-
Ventricular tachycardia	-	-	0.1-1	✔	-	-
Central Nervous System						
Abnormal dreaming	-	-	0.1-1	-	-	<1
Abnormal gait	<1	-	0.1-1	✔	-	-
Agitation	✔	-	0.1-1	0.1-1	-	-
Anosmia	✔	-	✔	-	-	-
Anxiety	-	≤0.1	0.1-1	0.1-1	0.1-0.2	<1
Asthenia	-	≤0.1	-	0.1-1	0.3-1.3	<1
Ataxia	<1	-	-	-	-	-
Chills	<1	-	-	0.1-11	0.1-0.2	<1
Confusion	✔	✔	0.1-1	0.1-1	✔	<1
Delirium	✔	-	-	-	-	-
Depersonalization	<1	-	-	-	-	-
Depression	<1	✔	0.1-1	0.1-1	0.1-0.2	<1

Adverse Events	Ciprofloxacin	Gemifloxacin	Levofloxacin	Moxifloxacin	Norfloxacin	Ofloxacin
Dizziness	<1	1.7	0.3-3	3	1.7-2.6	1-5
Drowsiness	<1	-	-	-	-	-
Encephalopathy	-	-	✔	-	-	-
Fatigue	-	<1	<1	0.1-1	<1	1-3
Fever	<1	-	✔	1.1	0.3-1	1-3
Hallucinations	<1	✔	0.1-1	0.1-1	-	<1
Headache	<1	4.2	0.3-6	4.2	2-2.8	1-9
Hyperkinesias	-	-	0.1-1	-	-	-
Hypertonia	-	-	0.1-1	-	-	-
Insomnia	<1	<1	4	1.9	0.1-0.2	3-7
Irritability	<1	-	-	-	-	-
Lethargy	<1	-	<1	0.1-1	<1	1-3
Lightheadedness	<1	-	-	✔	-	-
Malaise	<1	-	<1	0.1-1	<1	1-3
Manic reaction	<1	-	-	-	-	-
Migraine	<1	-	-	-	-	-
Nightmares	<1	-	0.1-1	-	-	-
Paranoia	-	-	✔	-	-	-
Paresthesia	<1	✔	0.1-1	0.1-1	0.3-1	<1
Peripheral neuropathy	✔	✔	✔	✔	✔	✔
Phobia	<1	-	-	-	-	-
Psychotic reactions	<1	✔	✔	✔	✔	-
Restlessness	<1	-	-	0.1-1	-	<1
Seizures	<1	✔	0.1-1	✔	✔	<1
Sleep disorder	-	-	0.1-1	-	0.1-0.2	-
Somnolence	<1	<1	0.1-1	0.1-1	0.3-1	1-3
Suicide attempt or ideation	-	-	✔	-	-	-
Tinnitus	<1	-	✔	0.1-1	-	<1
Tremor	<1	≤0.1	0.1-1	0.1-1	✔	<1
Weakness	<1	-	-	-	-	-
Vertigo	-	≤0.1	0.1-1	0.1-1	-	<1
Dermatological						
Cutaneous candidiasis	<1	-	-	-	-	-
Dermatitis	-	<1	-	0.1-1	✔	-
Eczema	-	≤0.1	-	-	-	-
Erythema multiform	-	✔	✔	-	✔	-
Erythema nodosum	<1	-	-	-	-	-

Adverse Events	Ciprofloxacin	Gemifloxacin	Levofloxacin	Moxifloxacin	Norfloxacin	Ofloxacin
Exfoliative dermatitis	-	-	-	-	✔	-
Flushing	<1	≤0.1	-	-	-	-
Hyperpigmentation	<1	-	-	-	-	-
Night sweats	-	-	-	0.1-1	-	-
Petechia	<1	-	-	-	-	-
Photosensitivity	<1	≤0.1	✔	✔	✔	✔
Pruritus	<1	<1	1	0.1-1	0.3-1	1-3
Rash	1	3.5	1	0.1-1	0.3-1	1-3
Stevens-Johnson syndrome	✔	-	✔	✔	✔	-
Sweating	<1	-	-	0.1-1	0.3-1	<1
Toxic epidermal necrolysis	✔	-	✔	✔	✔	-
Urticaria	<1	<1	0.1-1	0.1-1	0.1-0.2	<1
Gastrointestinal						
Abdominal pain/discomfort	<1	2.2	≤2	1.5	0.3-1.6	1-3
Anorexia	<1	<1	0.1-1	0.1-1	0.3-1	-
Constipation	✔	<1	3	<1	0.3-1	1-3
Diarrhea	1.6	5	5	6	0.3-1	1-4
Dry mouth	<1	<1	<1	0.1-1	0.3-1	1-3
Dyspepsia	✔	<1	2	1	0.3-1	<1
Dysphagia	<1	-	-	-	-	-
Esophagitis	-	-	0.1-1	-	-	-
Flatulence	<1	<1	-	0.1-1	0.3-1	1-3
Gastritis	-	<1	0.1-1	-	-	-
Gastroenteritis	-	-	0.1-1	0.1-1	-	-
Gastroesophageal reflux disease	-	-	-	0.1-1	-	-
Gastrointestinal bleeding	<1	-	-	0.1-1	-	-
Glossitis	-	-	0.1-1	-	-	-
Intestinal perforation	<1	-	-	-	-	-
Nausea	2.5	3.7	0.6-7	6.9	2.6-4.2	3-10
Oral candidiasis	<1	≤0.1	1	0.1-1	-	-
Painful oral mucosa	<1	-	-	-	-	-
Pancreatitis	-	-	0.1-1	-	✔	-
Pseudomembranous colitis	✔	✔	0.1-1	-	✔	✔
Stomatitis	-	-	0.1-1	-	✔	-
Taste alterations	<1	<1	✔	0.1-1	0.1-0.2	-
Vomiting	1	1.6	0.5-3	2.4	0.3-1	1-4
Genitourinary						

Adverse Events	Ciprofloxacin	Gemifloxacin	Levofloxacin	Moxifloxacin	Norfloxacin	Ofloxacin
Albuminuria	✔	-	-	-	1	≥1
Breast pain	<1	-	-	-	-	-
Candiduria	✔	-	-	-	✔	-
Crystalluria	✔	-	-	-	✔	-
Cylindruria	✔	-	-	-	-	-
Dysuria	-	-	-	0.1-1	-	<1
Genital irritation (pain or rash)	-	✔	-	-	-	<1
Genital moniliasis	-	<1	0.1-1	-	-	-
Glucosuria	-	-	-	-	✔	≥1
Hematuria	✔	-	-	-	-	≥1
Interstitial nephritis	<1	-	✔	✔	✔	-
Nephritis	<1	-	-	-	-	-
Polyuria	<1	-	-	-	-	<1
Proteinuria	-	-	-	-	1	≥1
Pyuria	-	-	-	-	✔	≥1
Renal Failure	<1	✔	0.1-1	0.1-1	✔	-
Renal function abnormal (non-specific)	-	-	0.1-1	✔	-	-
Urethral bleeding	<1	-	-	-	-	-
Urinary retention	<1	-	-	-	-	<1
Urine abnormalities	-	≤0.1	-	-	-	-
Vaginitis	<1	<1	<2	<1	-	1-5
Hematologic						
Acidosis	<1	-	-	-	-	-
Agranulocytosis	✔	-	-	✔	-	-
Anemia	<0.1	≤0.1	0.1-1	-	-	≥1
Aplastic anemia	-	-	✔	-	-	-
Eosinophilia	0.6	≤0.1	✔	0.1-1	1.5	≥1
ESR increased	-	-	-	-	-	≥1
Granulocytopenia	-	≤0.1	0.1-1	-	-	-
Hematocrit decreased	<0.1	0.3	-	0.1-1	0.6	-
Hematocrit increased	-	0.1	-	-	-	-
Hemoglobin decreased	<1	0.2	-	0.1-1	0.6	-
Hemoglobin increased	-	0.1	-	-	-	-
Hemolytic anemia	-	-	✔	-	-	-
Leukocytosis	<0.1	-	<1	0.1-1	-	≥ 1
Leukopenia	0.4	<1	✔	0.1-1	1.3	≥1
Lymphocytosis	-	-	-	-	-	≥1

Adverse Events	Ciprofloxacin	Gemifloxacin	Levofloxacin	Moxifloxacin	Norfloxacin	Ofloxacin
MCH increased	-	-	-	≥2	-	-
Monocytes increased	<0.1	-	-	-	-	-
Neutropenia	-	-	-	0.1-1	1	≥1
Neutrophils decreased	-	0.5	-	-	1.4	-
Neutrophils increased	-	0.5	-	≥2	-	-
Pancytopenia	0.1	-	✔	✔	-	-
Platelets decreased	0.1	0.2	-	-	1	-
Platelets increased	0.1	1	-	0.1-1	-	-
PT increased	<1	✔	✔	0.1-1	-	-
RBC decreased	-	0.1	-	≥2	-	-
RBC increased	-	0.1	-	-	-	-
Thrombocytosis	<1	-	-	0.1-1	1	≥1
Thrombocytopenia	<1	≤0.1	0.1-1	0.1-1	1	≥1
Hepatic						
Hepatic failure	✔	-	✔	✔	✔	-
Hepatic function abnormal	-	-	0.1-1	0.1-1	-	-
Hepatitis	<1	-	✔	✔	✔	-
Jaundice	<1	-	✔	✔	✔	-
Laboratory Test Abnormalities						
Albumin decreased	-	0.3	-	≥2	-	-
Alkaline phosphatase increased	0.8	<1	0.1-1	0.1-1	1.1	≥1
ALT increased	1.9	1.7	-	1.1	1.4	≥1
AST increased	1.7	1.3	-	1.1	1.4-1.6	≥1
Bilirubin abnormalities	0.3	≤0.1	-	0.1-1	-	-
BUN increased	0.9	0.3	-	0.1-1	✔	≥1
Calcium decreased	-	0.1	-	≥2	-	-
Calcium increased	-	<0.1	-	-	-	-
Cholesterol increased	✔	-	-	-	-	-
Creatinine phosphokinase increased	-	0.7	✔	-	-	-
GGT increased	-	≤0.1	-	1.1	-	-
Glucose abnormalities	<1	-	2	-	-	≥1
Hyperglycemia	-	<1	0.1-1	0.1-1	-	≥1
Hyperkalemia	-	-	0.1-1	-	-	-
Hypoglycemia	<0.1	-	0.1-1	0.1-1	-	-
Hypokalemia	-	-	-	1	-	-
Lactate dehydrogenase increased	-	≤0.1	-	-	-	-
LDH increased	0.4	-	<1	0.1-1	✔	-

Adverse Events	Ciprofloxacin	Gemifloxacin	Levofloxacin	Moxifloxacin	Norfloxacin	Ofloxacin
Liver enzymes increased	-	-	0.1-1	0.1-1	✔	-
Potassium alterations	✔	0.3	-	-	-	-
Serum amylase increased	<1	-	-	0.1-1-	-	-
Serum creatinine increased	1.1	0.2	-	0.1-1	✔	≥1
Serum lipase increased	<1	-	-	0.1-1	-	-
Sodium decreased	-	0.2	-	-	-	-
Sodium increased	-	0.1	-	-	-	-
Total protein decreased	-	0.1	-	-	-	-
Triglycerides increased	✔	-	-	0.1-1	-	-
Uric acid increased	<0.1	-	-	0.1-1	-	-
Musculoskeletal						
Achiness or myalgia	<1	≤0.1	0.1-1	0.1-1	✔	<1
Arthralgia or back pain	<1	≤0.1	0.1-1	0.1-1	0.3-1	<1
Joint stiffness	<1	-	-	-	-	-
Leg cramps	-	≤0.1	-	-	-	-
Muscle injury	-	-	✔	-	-	-
Muscle spasms	-	-	-	0.1-1	-	-
Neck or chest pain	<1	-	1	0.1-1	0.1-0.2	-
Rhabdomyolysis	-	-	✔	-	-	-
Skeletal pain	-	-	0.1-1	0.1-1	-	-
Tendinitis/tendon rupture	✔	✔	0.1-1	✔	-	-
Respiratory						
Bronchospasm	<1	-	-	0.1-1	-	-
Cough	-	-	-	-	-	<1
Dyspnea	<1	≤0.1	1	0.1-1	✔	-
Epistaxis	<1	-	0.1-1	-	-	<1
Hemoptysis	<1	-	-	-	-	-
Hiccough	<1	-	-	-	-	-
Laryngeal or pulmonary edema	<1	-	-	-	-	-
Pneumonia	-	≤0.1	-	-	-	-
Pneumonitis	-	-	✔	-	-	-
Pulmonary embolism	<1	-	-	-	-	-
Rhinorrhea	-	-	-	-	-	<1
Wheezing	-	-	-	0.1-1	-	-
Other						
Allergic reaction	<1	-	0.1-1	-	0.1-0.2	-
Anaphylactic reactions	✔	✔	✔	✔	✔	-

Adverse Events	Ciprofloxacin	Gemifloxacin	Levofloxacin	Moxifloxacin	Norfloxacin	Ofloxacin
Angioedema	<1	-	✔	✔	✔	<1
Dehydration	-	-	-	0.1-1	-	-
Edema	<1	≤0.1	1	0.1-1	0.1-0.2	<1
Eye Pain	<1	-	-	-	-	-
Foot Pain	<1	-	-	-	-	-
Fungal Infection	-	<1	-	0.1-1	-	-
Gout	<1	-	-	-	-	-
Hearing loss	<1	-	-	-	✔	<1
Hemorrhage	-	✔	-	-	-	-
Hypersensitivity	<1	✔	✔	✔	✔	✔
Injection site reaction	<1	-	1	0.1-1	-	-
Leukocytoclastic vasculitis	-	-	✔	-	-	<1
Lymphadenopathy	<1	-	-	-	-	-
Myasthenia gravis exacerbation	✔	✔	✔	✔	-	-
Multi-organ failure	-	-	✔	-	-	-
Pain	<1	≤0.1	-	0.1-1	-	<1
Pain in extremities	<1	-	-	0.1-1	-	<1
Pharyngitis	-	≤0.1	-	-	-	-
Phlebitis	<1	-	0.1-1	0.1-1	-	-
Serum sickness-like reaction	-	-	✔	-	-	-
Vasodilation	-	-	✔	-	-	<1
Visual disturbances	<1	≤0.1	✔	0.1-1	0.1-0.2	1-3

✔ Percent not specified
- Event not reported

Table 8. Boxed Warning for the Quinolones[3]

WARNING
Tendinitis and tendon rupture: Fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients (usually older than 60 years), in patients taking corticosteroid drugs, and in patients with kidney, heart, or lung transplants. **Myasthenia gravis:** Fluoroquinolones may exacerbate muscle weakness in persons with myasthenia gravis. Avoid using fluoroquinolones in patients with known history of myasthenia gravis.

VII. Dosing and Administration

The usual dosing regimens for the quinolones are listed in Table 9.

Table 9. Usual Dosing Regimens for the Quinolones[1-11]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ciprofloxacin	Bone and Joint Infections: Mild-to-moderate: Injection: 400 mg every 12 hours for ≥4 to 6 weeks Suspension/tablet (IR): 500 mg every 12 hours for ≥4 to 6 weeks Severe or complicated: Injection: 400 mg every 8 hours for ≥4 to 6 weeks Suspension/tablet (IR): 750 mg every 12 hours for ≥4 to 6 weeks Empiric Therapy for Febrile Neutropenic Patients: Injection: 400 mg every 8 hours for 5-7 days in combination with piperacillin Gonococcal Infections (Urethritis/Cervicitis): Suspension/tablet (IR): 250 mg in a single dose Infectious Diarrhea: Suspension/tablet (IR): 500 mg every 12 hours for 5-7 days Inhalational Anthrax: Injection: 400 mg every 12 hours for 60 days Suspension/tablet (IR): 500 mg every 12 hours for 60 days Intra-Abdominal Infections: Injection: 400 mg every 12 hours for 7-14 days Suspension/tablet (IR): 500 mg every 12 hours for 7-14 days	Inhalational Anthrax (Post-Exposure): 1 to 17 years of age: Injection: 10 mg/kg every 12 hours for 60 days Suspension/tablet (IR): 15 mg/kg every 12 hours for 60 days Urinary Tract Infections or Pyelonephritis: 1 to 17 years of age: Injection: 6-10 mg/kg every 8 hours for 10-21 days Suspension/tablet (IR): 10-20 mg/kg every 12 hours for 10-21 days	Injection: 10 mg/ml 200 mg/20 ml 200 mg/0.1 L 400 mg/40 ml 400 mg/0.2 L Suspension: 250 mg/5 ml 500 mg/5 ml Tablet (ER): 500 mg 1,000 mg Tablet (IR): 100 mg 250 mg 500 mg 750 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Pneumonia (Nosocomial): Injection: 400 mg every 8 hours for 10-14 days Prostatitis: Injection: 400 mg every 12 hours for 28 days Suspension/tablet (IR): 500 mg every 12 hours for 28 days Pyelonephritis: Oral (IR): 500 mg every 12 hours for 7 days Tablet (ER): 1,000 mg every 24 hours for 7 days Respiratory Tract Infections (Lower): Mild/moderate: Injection: 400 mg every 12 hours for 7-14 days Suspension/tablet (IR): 500 mg every 12 hours for 7-14 days Severe/complicated: Injection: 400 mg every 8 hours for 7-14 days Suspension/tablet (IR): 750 mg every 12 hours for 7-14 days Sinusitis: Injection: 400 mg every 12 hours for 10 days Suspension/tablet (IR): 500 mg every 12 hours for 10 days Skin and Skin-Structure Infections: Mild/moderate: Injection: 400 mg every 12 hours for 7-14 days Suspension/tablet (IR): 500 mg every 12 hours for 7-14 days Severe/complicated: Injection: 400 mg every 8 hours for 7-14 days Suspension/tablet (IR): 750 mg every 12 hours for 7-14 days Typhoid Fever: Suspension/tablet (IR): 500 mg every 12 hours for 10 days Urinary Tract Infections: Acute uncomplicated:		

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet (ER): 500 mg every 24 hours for 3 days Suspension/tablet (IR): 250 mg every 12 hours for 3 days Mild/moderate: Injection: 200 mg every 12 hours for 7-14 days Suspension/tablet (IR): 250 mg every 12 hours for 7-14 days Severe/complicated: Injection: 400 mg every 12 hours for 7-14 days Tablet (ER): 1,000 mg every 24 hours for 7-14 days Suspension/tablet (IR): 500 mg every 12 hours for 7-14 days		
Gemifloxacin	Acute Exacerbations of Chronic Bronchitis: 320 mg once daily for 5 days Pneumonia (Community-Acquired): 320 mg once daily for 5 to 7 days	Safety and efficacy in children have not been established.	Tablet: 320 mg
Levofloxacin	Acute Exacerbations of Chronic Bronchitis: 500 mg once daily for 7 days Inhalational Anthrax (Post-Exposure): 500 mg once daily for 60 days Pneumonia (Community-Acquired): 500 mg once daily for 7-14 days or 750 mg once daily for 5 days Pneumonia (Nosocomial): 750 mg once daily for 7-14 days Prostatitis: 500 mg once daily for 28 days Pyelonephritis: 750 mg once daily for 5 days or 250 mg once daily for 10 days Sinusitis: 750 mg once daily for 5 days or 500 mg once daily for 10-14 days Skin and Skin-Structure Infections: Complicated: 750 mg once daily for 7-14 days	Inhalational Anthrax (Post-Exposure): ≥6 months of age: >50 kg: 500 mg once daily for 60 days <50 kg: 8 mg/kg every 12 hours for 60 days	Injection: 25 mg/ml 250 mg/50 ml 500 mg/0.1 L 750 mg/0.15 L Solution: 250 mg/10 ml Tablet: 250 mg 500 mg 750 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Uncomplicated: 500 mg once daily for 7-10 days Urinary Tract Infections: Complicated:750 mg once daily for 5 days or 250 mg once daily for 10 days Uncomplicated: 250 mg once daily for 3 days		
Moxifloxacin	Acute Exacerbations of Chronic Bronchitis: 400 mg once daily for 5 days Intra-Abdominal Infections: 400 mg once daily for 5-14 days Pneumonia (Community-Acquired): 400 mg once daily for 7-14 days Sinusitis: 400 mg once daily for 10 days Skin and Skin-Structure Infections: Complicated: 400 mg once daily for 7-21 days Uncomplicated: 400 mg once daily for 7 days	Safety and efficacy in children have not been established.	Injection: 400 mg/0.25 L Tablet: 400 mg
Norfloxacin	Gonococcal Infections (Urethritis/Cervicitis): 800 mg in a single dose Prostatitis: 400 mg every 12 hours for 28 days Urinary Tract Infections: Complicated: 400 mg every 12 hours for 10-21 days Uncomplicated: 400 mg every 12 hours for 3-10 days	Safety and efficacy in children have not been established.	Tablet: 400 mg
Ofloxacin	Acute Exacerbations of Chronic Bronchitis: 400 mg every 12 hours for 10 days Cystitis: 200 mg every 12 hours for 3-7 days Gonococcal Infections	Safety and efficacy in children have not been established.	Tablet: 200 mg 300 mg 400 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	(Urethritis/Cervicitis): 400 mg in a single dose for 1 day Nongonococcal Infections (Urethritis/Cervicitis): 300 mg every 12 hours for 7 days Pelvic Inflammatory Disease: 400 mg every 12 hours for 10-14 days Pneumonia (Community-Acquired): 400 mg every 12 hours for 10 days Prostatitis: 300 mg every 12 hours for 6 weeks Skin and Skin-Structure Infections: 400 mg every 12 hours for 10 days Urinary Tract Infections: 200 mg every 12 hours for 10 days		

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the quinolones are summarized in Table 10.

Table 10. Comparative Clinical Trials with the Quinolones

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Nicodemo et al.[47] (1998) Ciprofloxacin 500 mg BID for 10 days vs levofloxacin 500 mg QD for 7 days	RCT, MC, DB Adult patients with uncomplicated skin and skin structure infections (SSSI)	N=272 7-10 days	Primary: Clinical success rate (defined as cure or improvement in signs and symptoms) Secondary: Microbiological eradication rate	Primary: Clinical success was achieved in 96.1% of those on levofloxacin and 93.5% on ciprofloxacin (95% confidence interval CI: –8.4 to 3.3). Secondary: Eradication was achieved in 93.0% of those on levofloxacin and 89.7% on ciprofloxacin (95% CI, –11.7 to 5.1). An adverse event related to the study medication was reported in 8.9% of the patients on levofloxacin and 8.2% of patients taking ciprofloxacin. Discontinuation due to an adverse event occurred in 5 patients taking levofloxacin and 2 patients taking ciprofloxacin.
Nichols et al.[48] (1997) Ciprofloxacin 500 mg BID for 10 days vs levofloxacin 500 mg QD for 7 days	RCT, MC, OL Adult patients with uncomplicated skin and skin structure infections (SSSI)	N=469 7-10 days	Primary: Clinical success rate (defined as cured or improvement in signs and symptoms) Secondary: Microbiological eradication rate by patient and by pathogen	Primary: Clinical success was achieved in 98% of those on levofloxacin and 94% on ciprofloxacin (95% CI, –7.7 to 0.7). Secondary: Eradication was achieved in 98% of those on levofloxacin and 89% on ciprofloxacin (95% CI, –14.5 to –2.7). The eradication rate of the most prevalent pathogen, *S aureus,* was 100% with levofloxacin and 87% with ciprofloxacin (95% CI, –20.2 to –5.1). The eradication rate of the second most prevalent pathogen, *S pyogenes,* was 100% with levofloxacin and 90% with ciprofloxacin (95% CI, –26.7 to 6.7). An adverse event related to the study medication was reported in 6% of the patients on levofloxacin and 5% of patients taking ciprofloxacin.
Vick Fragoso et al.[71]	RCT, OL, MC	N=804	Primary: Clinical response	Primary: Clinical cure (success) rates at TOC for the PP population were not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Moxifloxacin 400 mg IV once daily for at least 3 days followed by 400 mg orally for 7 to 21 days vs amoxicillin-clavulanate 1,000 mg-200 mg IV three times daily for at least 3 days followed by 500 mg-125 mg orally three times daily for 7 to 21 days The decision to switch from IV to oral therapy was based on clinical response.	Patients ≥18 years of age with complicated skin and skin-structure infections (cSSSI)	21 days	at TOC for the PP population Secondary: Clinical response at TOC for the ITT population and clinical response at TOC by indication, bacteriological success at TOC for the PP/MBE population	significantly different between the treatment groups: 80.6% for moxifloxacin compared with 84.5% for amoxicillin/clavulanate. These efficacy findings were supported by results for the ITT population: 72.7% for moxifloxacin compared with 74.8% for amoxicillin/clavulanate. Moxifloxacin was not inferior to amoxicillin/clavulanate for cSSSIs. Clinical success rates by indication were not significantly different among the treatment groups. The highest clinical success rates were for complicated erysipelas, abscess and surgical wound infection, and the lowest clinical success rates were for necrotizing fasciitis and diabetic foot infection. Clinical response rates in patients with a diabetic foot infection were similar between the two groups in patients with the most severe infections. Among the PP population, 19.4% of moxifloxacin- treated and 15.5% of amoxicillin/clavulanate-treated patients were clinical failures at TOC. There were no significant differences in bacteriological success rates at TOC in the PP/MBE population between moxifloxacin-treated patients (76.0%) and amoxicillin/clavulanate-treated patients (81.4%; 95% CI, -12.96 to 4.41; P=0.59).
Gastrointestinal Infections				
Kaushik et al.[66] (2010) Ciprofloxacin 20 mg/kg as a single dose vs azithromycin 20	RCT, OL Children 2 to 12 years of age with watery diarrhea for ≤24 hours and severe dehydration, who tested positive for *Vibrio cholerae* by hanging drop	N=180 3 days	Primary: Clinical success (resolution of diarrhea within 24 hours) and bacteriological success (cessation of excretion of *Vibrio cholerae* by day 3)	Primary: Clinical success was 94.5% with azithromycin compared to 70.7% with ciprofloxacin (RR 1.34; 95% CI, 1.16 to 1.54; P<0.001). Bacteriological success was 100% with azithromycin compared to 95.5% with ciprofloxacin (RR 1.05; 95% CI, 1.00 to 1.10; P=0.06). Secondary: Patients treated with azithromycin had a shorter duration of diarrhea compared to patients receiving ciprofloxacin (54.6 hours vs 71.5 hours,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg as a single dose	examination or culture of stool		Secondary: Duration of diarrhea, duration of excretion of *Vibrio cholerae* in stool, fluid requirement, and proportion of children with clinical or bacteriological relapse	respectively; P<0.001). Patients receiving azithromycin had a lesser duration of excretion of *Vibrio cholerae* than patients receiving ciprofloxacin (34.6 hours vs 52.1 hours; P<0.001). The amount of intravenous fluid was significantly less among patients who received azithromycin compared to those who received ciprofloxacin (4,704.7 ml vs 3,491.1 ml); P<0.001). The proportion of children with bacteriological relapse was comparable in both groups (6.7% with azithromycin vs 2.2% with ciprofloxacin; P=0.16). None of the children in either group had a clinical relapse.
Molina-Infante et al.[67] (2010) Levofloxacin 500 mg, omeprazole 20 mg, and amoxicillin 1g TID (OLA) vs clarithromycin 500 mg, omeprazole 20 mg, and amoxicillin 1g TID (OCA) vs omeprazole 20 mg and amoxicillin 1g BID for 5 days, followed by	RCT, OL Patients >18 years of age with *Helicobacter pylori* infection, determined by a positive urea breath test, histology, or rapid urease test	N=460 10 days	Primary: Eradication of *Helicobacter pylori* infection Secondary: Tolerance and compliance	Primary: The PP cure rates were 66% with OCA (95% CI, 57% to 74%), 82.4% with OLA (95% CI, 75% to 89%; P<0.05 vs OCA), 80.8% with OACM (95% CI, 73% to 88%; P<0.05 vs OCA), and 82.5% with OALM (95% CI, 78-91%; P<0.05 vs OCA). The ITT cure rates were 64% with OCA (95% CI, 55% to 73%), 80.8% with OLA (95% CI, 73% to 88%; P<0.05 vs OCA), 76.5% with OACM (95% CI, 69% to 85%; P<0.05 vs OCA), and 82.5% with OALM (95% CI, 75% to 89%; P<0.05 vs OCA). Secondary: No differences in adverse effects or compliance were demonstrated among treatments by questionnaire assessment. Minor or mild side effects were reported by 28% of patients without significant differences between treatments. No major adverse events were observed, though 9 patients discontinued therapy reportedly due to adverse events. A total of 97% of patients had complete adherence to antibiotic therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
omeprazole 10 mg, clarithromycin 500 mg, and metronidazole TID for 5 days (OACM) vs omeprazole 20 mg and amoxicillin 1g BID for 5 days, followed by omeprazole 20 mg, levofloxacin 500 mg, and metronidazole 500 mg TID for 5 days (OALM)				
Genitourinary Infections				
Fourcroy et al.[30] (2005) Ciprofloxacin immediate-release 250 mg BID for 3 days vs ciprofloxacin extended-release 500 mg QD for 3 days	RCT, MC, DB Adult female patients with uncomplicated urinary tract infections	N=1,037 3 days	Primary: Bacteriological eradication rates defined as $<10^4$ colony-forming units (CFU)/mL at 4-11 days Secondary: Bacteriological eradication rates at 28-42 days and clinical cure rates at 4-11days and at 25-50 days after therapy	Primary: Eradication at 4-11days was observed in 93.4% of patients on the extended-release formulation compared to 89.6% in the immediate-release formulation (95% CI, –0.99 to 8.59). Secondary: Eradication at 28-42 days was observed in 82.4% of patients on the extended-release formulation compared to 83.2% in the immediate-release formulation (95% CI, –8.00 to 6.40). Clinical cure at 4-11 days was observed in 85.7% of patients on the extended-release formulation compared to 86.1% in the immediate-release formulation (95% CI, –6.37 to 5.57). Clinical cure at 28-42 days was observed in 75.7% of patients on the extended-release formulation compared to 78.8% in the immediate-release formulation (95% CI, –10.60 to 4.40).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events were reported in 12.7% of patients on the extended-release formulation and 14.7% on the immediate-release formulation (P=NS). Seven patients on the extended-release formulation and 3 on the immediate-release formulation withdrew due to an adverse event.
Talan et al.[31] (2004) Ciprofloxacin immediate-release 500 mg BID for 7-10 days vs ciprofloxacin extended-release 1,000 mg QD for 7-10 days	RCT, MC, DB Adult patients with complicated urinary tract infections or acute uncomplicated pyelonephritis	N=1,035 7-14 days	Primary: Bacteriological eradication rates (defined as $<10^4$ CFU/mL) and clinical cure rates at 5-11 days and at 28-42 days after therapy Secondary: Adverse events	Primary: Eradication at 5-11 days was observed in 89% of patients on the extended-release formulation compared to 85% in the immediate-release formulation (95% CI, –2.4 to 10.3). Eradication at 28-42 days was observed in 69.3% of patients on the extended-release formulation compared to 61.2% in the immediate-release formulation (95% CI, –0.8 to 18.6). Clinical cure at 5-11 days was observed in 97% of patients on the extended-release formulation compared to 94% in the immediate-release formulation (95% CI, –1.2 to 6.9). Clinical cure at 28-42 days was observed in 82.9% of patients on the extended-release formulation compared to 80.7% in the immediate-release formulation (95% CI, –5.4 to 10.4). Secondary: Drug-related adverse events were reported in 13.2% of patients on the extended-release formulation and 13.5% on the immediate-release formulation. The most commonly reported adverse reactions were nausea, diarrhea, vaginal moniliasis, headache and dizziness. Sixteen patients on the extended-release formulation and 12 on the immediate-release formulation withdrew due to an adverse event.
Henry et al.[32] (2002) Ciprofloxacin immediate-release 250 mg BID for 3 days vs	RCT, MC, DB Adult female patients with uncomplicated urinary tract infections	N=891 3 days	Primary: Bacteriological eradication rates (defined as $<10^4$ CFU/mL) and clinical cure rates at 4-11 days and at 25-50 days after therapy	Primary: Eradication at 4-11 days was observed in 94.5% of patients on the extended-release formulation compared to 93.7% in the immediate-release formulation (95% CI, –3.5 to 5.1). Eradication at 28-42 days was observed in 85.8% of patients on the extended-release formulation compared to 81.3% in the immediate-release formulation (95% CI, –1.9 to 12.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ciprofloxacin extended-release 500 mg QD for 3 days			Secondary: Adverse events	Clinical cure at 4-11 days was observed in 95.5% of patients on the extended-release formulation compared to 92.7% in the immediate-release formulation (95% CI, –1.6 to 7). Clinical cure at 28-42 days was observed in 89.0% of patients on the extended-release formulation compared to 86.6% in the immediate-release formulation (95% CI, –3.1 to 8.8). Secondary: Drug-related adverse events were reported in 10.4% of patients on the extended-release formulation and 9.2% on the immediate-release formulation.
Richard et al.[33] (1998) Ciprofloxacin 500 mg BID vs levofloxacin 250 mg QD vs lomefloxacin 400 mg QD	MA Adult patients with acute uncomplicated pyelonephritis	N=186 (2 trials) 7-14 days	Primary: Eradication rates, defined as $<10^4$ CFU/mL at 5-9 days Secondary: Clinical cure rate, defined as complete resolution of symptoms	Primary: Eradication was observed in 95% of the patients on levofloxacin, 94% in patients on ciprofloxacin, and 95% in patients on lomefloxacin. Secondary: Clinical cure was observed in 92% of the patients on levofloxacin, 88% in patients on ciprofloxacin, and 80% in patients on lomefloxacin. An adverse event related to the study medication was reported in 2% of the patients on levofloxacin, 8% of patients taking ciprofloxacin, and 5% of patients taking lomefloxacin. One patient taking lomefloxacin withdrew due to an adverse event.
Bundrick et al.[34] (2003) Ciprofloxacin 500 mg BID vs levofloxacin 500 mg QD	RCT, MC, DB Adult male patients with a history of chronic prostatitis	N=377 28 days	Primary: Clinical success and microbiological eradication rates Secondary: Adverse events	Primary: Clinical success was observed in 75.0% of patients taking levofloxacin and 72.8% of those taking ciprofloxacin (95% CI, –13.27 to 8.87). Eradication was observed in 75.0% of patients taking levofloxacin and 76.8% of those taking ciprofloxacin (95% CI, –8.98 to 12.58). Secondary: Drug-related adverse effects were reported in 44.2% of patients taking levofloxacin and 37.2% taking ciprofloxacin. The most frequently

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reported adverse reaction was gastrointestinal in nature.
Arredondo-Garcia et al.[35] (2004) Ciprofloxacin 250 mg BID for 3 days vs norfloxacin 400 mg BID for 7 days vs sulfamethoxazole-trimethoprim (SMX-TMP) 160/800 mg for 7 days	RCT, MC, OL Adult female patients with uncomplicated urinary tract infection (cystitis)	N=455 3-7 days	Primary: Clinical resolution rates at early follow-up (5-9 days after treatment) and at late follow-up (4-6 weeks after treatment), bacteriological cure rates at early follow-up and at late follow-up and successful overall efficacy (bacteriological cure + clinical resolution) at early follow-up and at late follow-up Secondary: Adverse events	Primary: At early follow-up, resolution rates were 88.7% with ciprofloxacin, 84.1% with norfloxacin, and 86.4% on SMX-TMP. There were no significant differences between the three treatment groups. At late follow-up, resolution rates were 83.5% with ciprofloxacin, 82.2% with norfloxacin, and 81.5% on SMX-TMP. There were no significant differences between the three treatment groups. At early follow-up, cures rates were 91.8% with ciprofloxacin, 86.9% with norfloxacin, and 85.2% on SMX-TMP. There were no significant differences between the three treatment groups. At late follow-up, cures rates were 83.5% with ciprofloxacin, 81.3% with norfloxacin, and 81.5% on SMX-TMP. There were no significant differences between the three treatment groups. Success rates at early follow-up were 83.5% with ciprofloxacin, 78.5% with norfloxacin, and 81.5% on SMX-TMP. There were no significant differences between the three treatment groups. Success rates at early follow-up were 77.3% with ciprofloxacin, 80.4% with norfloxacin, and 75.3% on SMX-TMP. There were no significant differences between the three treatment groups. Secondary: More patients reported drug-related adverse reactions with SMX-TMP (7.3%) compared to ciprofloxacin (0.7%) and norfloxacin (2.6%).
Schaeffer et al.[36] (1992) Ciprofloxacin 500 mg BID vs	PRO, RCT, OL Adult patients with complicated urinary tract infection	N=72 10-21 days	Primary: Clinical cure rates, defined as complete resolution of symptoms and eradication of the infecting	Primary: Clinical cure rates were 72% for those on norfloxacin and 79% on ciprofloxacin (P=0.56).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
norfloxacin 400 mg BID			organism(s) after 2-4 days and 5-9 days of therapy	
Auquer et al.[38] (2002) Ciprofloxacin 500 mg once vs norfloxacin 400 mg BID for 3 days	RCT, MC, DB Adult female patients with uncomplicated urinary tract infection	N=226 3 days	Primary: Clinical cure and bacterial eradication (defined as $<10^5$ CFU/mL of a gram-negative bacteria or $<10^4$ CFU/mL of a gram-positive bacteria) at day 7	Primary: After 7 days of treatment, clinical cure were observed in 91.2% of patients on ciprofloxacin and 93.8% in patients on norfloxacin. After 7 days of treatment, eradication was observed in 91.2% of patients on ciprofloxacin and 92.0% in patients on norfloxacin. Statistical analysis yielded significant results in favor of the hypothesis of equivalence between the two treatment groups (P=0.0062). Drug-related adverse effects were reported in 17 patients taking ciprofloxacin and 13 taking norfloxacin. The most frequently reported adverse reaction was gastrointestinal in nature.
Perea et al.[37] (1989) Ciprofloxacin 500 mg BID vs ofloxacin 200 mg BID	RCT, DB Adult patients with nongonococcal urethritis	N=95 7 days	Primary: Clinical cure rates, defined as lack of symptoms and fewer than 5 polymorphonuclear leukocytes (PMNL) in a Gram-stained urethral smear	Primary: Clinical cure rates 2 weeks after treatment was observed in 75% of patients on ciprofloxacin and 74% of those on ofloxacin.
Raz et al.[39] (2000) Ciprofloxacin 250 mg BID vs ofloxacin 200 mg BID	RCT, MC, DB Adult female patients with complicated lower urinary tract infection	N=465 7 days	Primary: Bacteriological success, defined as sterile urine culture at 5-9 days Secondary: Bacteriological success at 28-42 days and clinical resolution after 5-9	Primary: Bacteriological success at 5-9 days was observed in 87.2% of the patients taking ofloxacin and 90.1% of patients taking ciprofloxacin (95% CI, –4.4 to 10.0). Secondary: Bacteriological success at 28-42 days was observed in 76.1% of the patients taking ofloxacin and 77.1 % of patients taking ciprofloxacin (95% CI, –9.2 to 10.5). Clinical cure at 5-9 days was observed in 97.2% of the patients taking

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			days and at 28-42 days	ofloxacin and 97.2% of patients taking ciprofloxacin (95% CI, –3.8 to 3.9). Clinical cure at 28-42 days was observed in 87.3% of the patients taking ofloxacin and 87.4% of patients taking ciprofloxacin (95% CI, –8.1 to 7.4). Drug-related adverse effects were reported in 10.9% of the women taking ciprofloxacin and 13.4% taking ofloxacin. The most frequently reported adverse reaction was gastrointestinal in nature. Thirteen women on ciprofloxacin and 16 on ofloxacin withdrew from the study due to adverse effects.
McCarty et al.[40] (1999) Ciprofloxacin 100 mg BID for 3 days vs ofloxacin 200 mg BID for 3 days vs SMX-TMP 160/800 BID for 3 days	RCT, MC, DB Adult female patients with acute urinary tract infection	N=866 3 days	Primary: Clinical resolution rates at early follow-up (3-10 days after treatment) and at late follow-up (4-6 weeks after treatment) and bacteriological eradication rates (defined as $<10^3$ CFU/mL) at early follow-up and at late follow-up Secondary: Adverse events	Primary: At early follow-up, resolution rates were 93% with ciprofloxacin, 96% with ofloxacin, and 95% on SMX-TMP. There were no significant differences between the three treatment groups. At late follow-up, resolution rates were 91% with ciprofloxacin, 89% with ofloxacin, and 91% on SMX-TMP. There were no significant differences between the three treatment groups. At early follow-up, eradication rates were 94% with ciprofloxacin, 97% with ofloxacin, and 92.5% on SMX-TMP. There were no significant differences between the three treatment groups. At late follow-up, eradication rates were 89% with ciprofloxacin, 87% with ofloxacin, and 84% on SMX-TMP. There were no significant differences between the three treatment groups. Secondary: More patients reported drug-related adverse reactions with SMX-TMP (35%) compared to ciprofloxacin (26%). Adverse reactions were reported in 34% of patients taking ofloxacin. Significantly more patients taking SMX-TMP (9) withdrew due to adverse reactions compared to ciprofloxacin (2) or ofloxacin (1; P<0.02).
Peterson et al.[52] (2008)	RCT, DB, MC	N=1109	Primary: Microbiological	Primary: At end of therapy, eradication rates in the modified intent-to-treat

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Levofloxacin 750 mg IV/PO once daily for 5 days vs ciprofloxacin 400 mg IV or 500 mg orally twice daily for 10 days	Patients with complicated urinary tract infections (cUTI) or acute pyelonephritis (AP)	45 days	eradication and clinical cure	population were 79.8% for levofloxacin and 77.5% for ciprofloxacin-treated patients (95% CI, -8.8% to 4.1%). In the microbiologically evaluable population, eradication rates were 88.3% for levofloxacin and 86.7% for ciprofloxacin-treated patients (95% CI, -7.4% to 4.2%). Clinical success at the end-of-therapy (EOT) was 91.3% and 87.1% for levofloxacin-treated and ciprofloxacin-treated patients, respectively (95% CI, -9.6% to 1.2%). At the post-therapy assessment, clinical response was 86.4% for levofloxacin-treated and 88.4% for ciprofloxacin-treated patients (95% CI, -3.9% to 7.8%). Clinical success rates for cUTI (78.9% versus 79.9%) or AP patients (86.2% versus 80.6%) were similar for levofloxacin and ciprofloxacin, respectively.
Klausner et al.[53] (2007) Levofloxacin 750 mg IV/PO once daily for 5 days vs ciprofloxacin 400 mg IV and/or 500 mg orally twice daily for 10 days	RCT, DB Adult male and female patients with clinical signs and symptoms of complicated urinary tract infections (cUTI) and acute pyelonephritis (AP)	N=311 45 days	Primary: Microbiologic eradication post-therapy (study days 15-22) Secondary: Clinical response, safety, tolerability	Primary: In the modified intent-to-treat (mITT) population, 83% of levofloxacin-treated and 79.6% of ciprofloxacin-treated patients achieved microbiological eradication (95% CI -14.4%, 7.6%). In the microbiologically evaluable (ME) population 92.5% of levofloxacin-treated vs 93.4% of ciprofloxacin-treated patients achieved microbiologic eradication (95% CI -7.1%, 8.9%). Secondary: Clinical success was achieved in 86.2% vs 80.6% (mITT) and in 92.5% vs 89.5% (ME) of levofloxacin-treated and ciprofloxacin-treated patients, respectively. *Escherichia coli* was the most commonly uropathogen that was isolate. Few (2.1%) of the pathogens were fluoroquinolone-resistant. Adverse events were similar to those seen previously with both agents.
Redman et al.[81]	RCT, DB	N=1,179	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) Study 1 Levofloxacin 250 mg IV once daily vs doripenem 500 mg IV every 8 hours Study 2 Doripenem 500 mg IV every 8 hours After a minimum of 3 days of IV therapy, investigators could switch patients from IV therapy to oral levofloxacin 250 mg daily.	Patients ≥18 years of age with complicated urinary tract infections (cUTI) and pyelonephritis	42 days after the last dose	Microbiological response at the test-of-cure (TOC) visit (5-11 days after the last dose); clinical cure rates	Microbiological eradication rates in the microbiologically evaluable patient population at the TOC visit were 82.1% with doripenem and 83.4% with levofloxacin in study 1, and 83.6% with doripenem in study 2. The combined analysis demonstrated that doripenem was non-inferior to levofloxacin. Microbiological eradication rates in the mMITT population at the TOC visit were 79.2% with doripenem and 78.2% with levofloxacin in study 1, and 82.5% with doripenem in study 2.The combined analysis in the mMITT population demonstrated that doripenem was non-inferior to levofloxacin. The pooled microbiological eradication rates in the microbiologically evaluable populations at the TOC and EOT visits from both studies were 99.8% with doripenem and 88.4% with levofloxacin (95% CI, 7.2% to 15.6%). These results suggest that the eradication preceded a switch from IV to oral levofloxacin therapy. Clinical cure rates for the combined clinically evaluable population at the TOC visit were 95.1% with doripenem and 90.2% with levofloxacin in study 1, and 93.0% with doripenem in study 2. The pooled clinical cure rates in the clinically evaluable populations at the TOC and EOT visits showed that clinical improvement preceded a switch to oral levofloxacin; 98.9% with doripenem and 93.2% with levofloxacin in study 1, and 99.6% with doripenem in study 2.
Naber et al.[80] (2009) Levofloxacin 250 mg IV once daily vs doripenem 500 mg IV every 8 hours	RCT, MC, DB Patients ≥18 years of age with complicated lower urinary tract infections (cUTI) or pyelonephritis who required initial treatment with a parenterally	N=753 Up to 14 days	Primary: Microbiological cure rate in the ME and mMITT population Secondary: Clinical cure rate at the TOC visit for the CE population and the	Primary: The ME population achieved microbiological cure rates of 82.1% and 83.4% with doripenem and levofloxacin, respectively. Patients in the mMITT population achieved microbiological cure rates of 79.2% and 78.2%, respectively. Doripenem was not therapeutically inferior to levofloxacin for the treatment of cUTI or pyelonephritis. In the ME population, the microbiological cure rates at the EOT IV were 100% for the doripenem-treated patients and 88% for the levofloxacin-treated patients (P<0.001). The non-inferior response demonstrated for the doripenem-treated patients at the TOC visit could be attributed to the IV

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients in both treatment arms were eligible to switch to oral levofloxacin after 3 days of IV therapy to complete a 10-day treatment course if they demonstrated significant clinical and microbiological improvements.	administered antibacterial agent		microbiological cure rate for the ME patients infected with *E. coli*	portion of the therapeutic regimen, independently of a switch to oral levofloxacin. Secondary: In the CE population, the clinical cure rates at EOT IV were 98.3% and 93.2% in the doripenem and levofloxacin arms, respectively. At the TOC visit, the clinical cure rates were 95.1% and 90.2%, respectively (95% CI, 0.2% to 9.6%). Clinical cure rates at the LFU visit of 90.8% for the doripenem-treated patients and 95.2% for the levofloxacin-treated patients who were CE were sustained. For the patients who received the IV study drug only, the clinical cure rates at the TOC visit were 78.1% with doripenem and 52.3% with levofloxacin. The microbiological cure rates for *E. coli* infections of ME patients at the TOC visit were 84.4% for the doripenem arm and 87.2% for the levofloxacin arm (P=0.83).
Heystek et al.[69] (2009) Moxifloxacin 400 mg QD for 14 days vs doxycycline 100 mg BID for 14 days, metronidazole 400 mg TID for 14 days, ciprofloxacin 500 mg as a single dose	RCT, MC, DB Women with uncomplicated pelvic inflammatory disease (PID)	N=434 14 days	Primary: Clinical success 2 to 14 days posttreatment (clinical cure and improvement combined) Secondary: Clinical cure rate at 2 to 14 days posttreatment, clinical success rate at 21 to 35 days posttreatment (clinical failures at day 2 to 14	Primary: Clinical success rates 2 to 14 days following treatment were 96.6% with moxifloxacin and 98% with the comparator regimen in the PP population (95% CI -4.5 to 1.6) Clinical success rates were 77.0% with moxifloxacin and 76.7% with the comparator regimen in the ITT population (95% CI, -5.8 to 6.9). Moxifloxacin was found to be non-inferior to the comparator arm. Secondary: At 2 to 14 days posttreatment, clinical cure rates were 81.5% with moxifloxacin and 83.2% with the comparator regimen in the PP population (95% CI -9.2 to 5.1). Clinical cure rates were 64.7% with moxifloxacin and 65.0% with the comparator regimen in the ITT population (95% CI, -7.5 to 7.0). Clinical success rates 21 to 35 days following treatment were 93.8% with moxifloxacin and 91.3% with the comparator regimen in the PP

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			posttreatment carried forward for follow-up), bacteriological response	population (95% CI -3.8 to 7.4). Clinical success rates were 60.1% with moxifloxacin and 56.8% with the comparator regimen in the ITT (95% CI, -5.8 to 9.1). In the MBV population, overall bacteriological success rates at 2 to 14 days posttreatment were similar in the two treatment groups (moxifloxacin: 92.5%, comparator 88.2%, P=0.52).
Judlin et al.[70] (2010) Moxifloxacin 400 mg QD for 14 days vs levofloxacin 500 mg QD and metronidazole 500 mg BID for 14 days All patients positive for *Neisseria gonorrhoeae* also received ceftriaxone 250 mg IM as a single dose.	RCT, DB, MC Women with uncomplicated pelvic inflammatory disease (PID)	N=460 6 weeks	Primary: Clinical cure at test-of-cure (TOC) visit (7-14 days after last dose of study drug) in the per protocol population Secondary: Clinical response during therapy and at the 4 week follow-up, microbiological response at TOC, safety	Primary: The clinical cure rate at the TOC visit was 78.4% with moxifloxacin and 81.6% with levofloxacin-metronidazole (P=0.460). Moxifloxacin was found to be non-inferior to levofloxacin-metronidazole. Secondary: Bacteriological success rates were comparable between treatment arms (MBV population: 12.2% of total study population; moxifloxacin: 90.0%; levofloxacin-metronidazole: 84.6%; 95% CI, -12.7 to 20.3). In the ITT analysis 56.6% of patients receiving moxifloxacin and 56.9% of patients receiving levofloxacin-metronidazole experienced adverse events. A total of 4% of patients receiving moxifloxacin and 5.2% of patients receiving levofloxacin-metronidazole experienced at least one drug-related adverse event that resulted in premature termination of the study drug.
Ross et al.[41] (2006) Moxifloxacin 400 mg QD for 14 days vs ofloxacin 400 mg BID in combination with metronidazole	RCT, MC, DB Women with uncomplicated pelvic inflammatory disease (PID)	N=741 14 days	Primary: Clinical resolution rates at 5-24 days post-therapy Secondary: Clinical resolution at 28-42 days post-therapy and bacteriological response at 5-24	Primary: Clinical resolution was observed in 90.2% of patients on moxifloxacin and 90.7% of patients on ofloxacin/metronidazole (95% CI, –5.7 to 4.0). Secondary: Clinical resolution at 28-42 days was observed in 85.8% of patients on moxifloxacin and 87.9% of patients on ofloxacin/metronidazole (95% CI, –8.0 to 3.1). Bacteriological response at 5-24 days was observed in 87.5% of patients on moxifloxacin and 82.1% of patients on ofloxacin/metronidazole (95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
500 mg BID			days	CI, –8.3 to 8.8). Significantly more patients taking ofloxacin/metronidazole reported a drug-related adverse event (30.9%) than those taking moxifloxacin (22.5%, P=0.01). Most commonly reported adverse events were gastrointestinal in nature. Withdrawals due to a drug-related adverse event occurred in 6.3% of patients receiving moxifloxacin compared to 5.0% in the ofloxacin/metronidazole group (P=0.41).
Boothby et al.[68] (2010) Moxifloxacin 400 mg QD for 14 days vs ofloxacin 400 mg BID and metronidazole 400 mg BID	RETRO Women with uncomplicated pelvic inflammatory disease (PID)	N=741 14 days	Primary: Clinical response (significant improvement or response, marginal improvement, or no change/worse) Secondary: Tolerability	Primary: There was no significant difference in clinical response rates with moxifloxacin compared to ofloxacin-metronidazole (significant improvement/resolved: 70% and 77%, respectively; marginal improvement: 11% and 3%, respectively; no change/worse: 18% and 20%; P=0.14). Secondary: For those patients who attended clinic for follow-up, adverse events occurred in 16% of patients receiving moxifloxacin and in 19% of patients receiving ofloxacin-metronidazole. Most were gastrointestinal in nature.
Rafalsky et al.[29] (2006) Quinolones (ciprofloxacin, ciprofloxacin extended-release, fleroxacin, gemifloxacin, levofloxacin, norfloxacin, ofloxacin, pefloxacin, or rufloxacin)	MA Women with uncomplicated acute cystitis	N=7,535 (11 Trials) Variable duration	Primary: Clinical response, bacteriological eradication, and clinical success (cure or improvement) + bacteriological eradication	Primary: For all primary endpoint measures in all 11 trials, there were no significant differences in clinical or microbiological efficacy between the quinolones.
Respiratory Infections				
Nouira et al.[72] (2010)	RCT, DB	N=170	Primary: Hospital death and	Primary: Combined hospital death and additional antibiotic prescription rates were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ciprofloxacin 750 mg twice daily for 10 days vs sulfamethoxazole-trimethoprim 800/160 mg twice daily for 10 days	Patients ≥40 years of age with an acute exacerbation of COPD requiring mechanical ventilation	10 days	need for an additional course of antibiotics Secondary: Duration of mechanical ventilation, length of hospital stay, and exacerbation-free interval (EFI)	similar in the 2 groups (16.4% vs 15.3% in the sulfamethoxazole-trimethoprim vs ciprofloxacin group; 95% CI, -9.8% to 12.0%; P=0.832). During the study, 15 patients died in the hospital, 7 (8.2%) in the sulfamethoxazole-trimethoprim group and 8 (9.4%) in the ciprofloxacin group (P>0.05). Secondary: The mean EFI was similar in both treatment groups (83 days vs 79 days in the sulfamethoxazole-trimethoprim vs ciprofloxacin group; P=0.41). Of 38 patients initially receiving noninvasive ventilation in the sulfamethoxazole-trimethoprim group, 17 (45%) were secondarily intubated versus 13 (34%) in the ciprofloxacin group (P=0.347). The duration of mechanical ventilation and length of hospital stay were similar in the 2 study groups. Adverse events were minor and comparably distributed in both treatment groups.
Sethi et al.[44] (2004) Gemifloxacin 320 mg QD for 5 days vs levofloxacin 500 mg QD for 7 days	RCT, MC DB Patients >40 years of age with acute exacerbation of chronic bronchitis	N=360 5 days	Primary: Clinical success rate (defined as resolution or significant improvement of symptoms) at days 14-21 Secondary: Clinical success rate at days 9-11 and at 28-35 days, bacteriologic eradication rate at 9-11, 14-21 and at 28-35 days	Primary: Clinical success at 14-21 days was observed in 88.2% of patients treated with gemifloxacin and 85.1% in those treated with levofloxacin (95% CI, –4.67 to 10.72). Secondary: Clinical success at 9-11 days was observed in 97.5% of patients treated with gemifloxacin and 93.5% in those treated with levofloxacin (95% CI, –0.61 to 8.51). Clinical success at 28-35 days was observed in 83.7% of patients treated with gemifloxacin and 78.4% in those treated with levofloxacin (95% CI, –3.83 to 14.34). Eradication at 9-11 days was observed in 87.5% of patients treated with gemifloxacin and 90.4% in those treated with levofloxacin. Eradication at 14-21 days was observed in 78.4% of patients treated with gemifloxacin and 85.7% in those treated with levofloxacin. Eradication at 28-35 days was observed in 77.8% of patients treated with gemifloxacin and 70.5% in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				those treated with levofloxacin. Adverse events were reported in 39.6% of patients taking gemifloxacin and 33.7% of patients taking levofloxacin. Withdrawals due to adverse events occurred in 4 patients on gemifloxacin and 10 patients taking levofloxacin.
Noel et al.[65] (2008) Levofloxacin 10 mg/kg BID vs amoxicillin-clavulanate (amoxicillin 45 mg/kg) BID	RCT, MC, SB Children 6 months to 5 years of age with recurrent and/or persistent acute otitis media (AOM) that was unchanged or worsened after ≥3 days of treatment with an antimicrobial regimen used to treat AOM	N=1,650 27 days	Primary: Clinical cure rates at visit 3 (2-5 days post-therapy) Secondary: Clinical cure rate at visit 4 (10-17 days post therapy), clinical success (cured or improved) at visits 3 and 4, safety	Primary: Clinical cure rates were 72.4% with levofloxacin and 69.9% with amoxicillin-clavulanate (95% CI, -7.37 to 2.46). Levofloxacin was found to be non-inferior to amoxicillin-clavulanate. Cure rates were similar among different age groups: ≤24 months: 68.9% vs 66.2%, respectively (95% CI, -9.36 to 4.03); >24 months: 76.9% vs 75.1%; respectively (95% CI, -8.94 to 5.28). Secondary: Clinical cure rates at visit 4 were 74.9% for levofloxacin and 73.9% for amoxicillin-clavulanate (95% CI, -5.55 to 3.54). Clinical success rates at visit 3 were 94.0% for levofloxacin and 90.8% for amoxicillin-clavulanate (95% CI, -6.02 to -0.29). Clinical success rates at visit 4 were 83.6% for levofloxacin and 80.4% for amoxicillin-clavulanate (95% CI, -7.18 to 0.81). There was no difference observed between treatments regarding frequency or type of adverse events. Most adverse events were mild or moderate in severity (97% levofloxacin; 96% amoxicillin-clavulanate) with diarrhea being the most frequent.
Griffin et al.[78] (2010) Levofloxacin vs azithromycin or	RETRO Patients with *Legionella* pneumonia	N=39 Variable duration	Primary: Time to clinical stability (TCS) and length of hospital stay (LOS)	Primary: The mean TCS for the macrolide group was 5.1 days and 4.3 days for the levofloxacin group (P=0.43). The mean LOS for the macrolide group was 12.7 days and 8.9 days for the levofloxacin group (P=0.10).

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clarithromycin				
Mokabberi et al.[75] (2010) Levofloxacin 500 mg IV QD vs doxycycline 100 mg IV BID Patients were allowed to switch from IV to oral therapy at the discretion of the physician.	PRO, DB, RCT Patients ≥18 years of age with pneumonia requiring hospitalization	N=65 2 months	Primary: Response to treatment, failure to treatment and complications, length of stay	Primary: Efficacy of treatment was not significantly different between the treatment groups (P=0.844). There were two failures in the levofloxacin group and one failure in the doxycycline group (P=0.893). Two patients in the levofloxacin group had side effects (mild diarrhea), while no side effects were noted for doxycycline (P=0.375). The mean time to change from IV to oral for levofloxacin group was 2.73 and 2.88 days for doxycycline group (P=0.647). Length of stay was 5.7 days for levofloxacin and 4.0 days for doxycycline (P<0.001).
Anzueto et al.[42] (2006) Levofloxacin 500 mg IV then by mouth for 7-14 days vs moxifloxacin 400 mg IV then by mouth for 7-14 days All patients received IV study medications and were converted to	RCT, PRO, DB Patients ≥65 years of age with community-acquired pneumonia	N=394 7-14 days	Primary: Clinical cure rate (defined as disappearance of symptoms or improvement that additional/ alternative therapy was not necessary) at 5-21 days after therapy Secondary: Clinical recovery (defined as disappearance to acute symptoms or reduction in severity or number	Primary: Clinical cure was observed in 92.9% of the patients taking moxifloxacin and 87.9% of those on levofloxacin (95% CI, –1.9 to 11.9, P=0.2). Secondary: Significantly more patients taking moxifloxacin (97.9%) exhibited clinical recovery at 3-5 days than those on levofloxacin (90.0%, 95% CI: 1.7 to 14.1; P=0.01). Bacteriologic eradication was observed in 81.0% of patients taking moxifloxacin and 75.0% in patients taking levofloxacin (P=0.9). The total duration of hospital stay was 7.5 days ± 4.2 days on moxifloxacin compared to 7.5 days ± 4.6 days with levofloxacin (P=0.95). For patients in the intensive care unit (ICU), total duration of stay was similar between treatment groups. The rate of drug-related and serious adverse events was comparable between the two treatments. Ten patients on moxifloxacin and 7 taking

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oral therapy after ≥2 days if they exhibited response to therapy and were able to tolerate oral food and medications.			of symptoms) during therapy (3-5 days after start or therapy), bacteriologic eradication, and health resource utilization	levofloxacin withdrew due to a drug-related adverse event. There was no difference in mortality in the two treatment groups (P=0.5).
Leroy et al.[43] (2005) Levofloxacin 500 mg IV, followed by oral therapy BID for 10-14 days vs ofloxacin 200 mg IV BID and cefotaxime IV TID, followed by oral therapy ofloxacin 200 mg BID for 10-14 days Patients were converted to oral therapy if appropriate. Monotherapy with ofloxacin in the cefotaxime-ofloxacin group was possible if the causal organism was *S pneumoniae*	RCT, MC, OL Adult patients with community-acquired pneumonia requiring ICU admission	N=398 10-14 days	Primary: Clinical cure rate (defined as disappearance of symptoms or improvement that additional/ alternative therapy was not necessary) at 1 day after end of therapy Secondary: Bacteriologic response (eradication of causative pathogen) at 1 day after end of therapy, clinical and bacteriologic response at 21-45 days, mortality rates and length of stay in the ICU	Primary: Clinical cure was observed in 79.1% of the patients taking levofloxacin and 79.5% of those on ofloxacin/cefotaxime (95% CI, –10.79 to 9.97). Secondary: Bacteriologic response 1 day after end of therapy was observed in 73.7% of the patients taking levofloxacin and 77.5% of those on ofloxacin/cefotaxime (P=0.59). Clinical cure at 21-45 days after treatment was observed in 68.8% of the patients taking levofloxacin and 70.9% of those on ofloxacin/cefotaxime (95% CI, –14.53 to 10.25). Bacteriologic response 21-45 days after end of therapy was observed in 62.5% of the patients taking levofloxacin and 65.6% of those on ofloxacin/cefotaxime (P=0.71). Mortality rates were 12.1% with levofloxacin and 12.6% with ofloxacin/cefotaxime (P=0.89). The total duration of ICU stay was 11.9 days ± 9.1 days on levofloxacin compared to 12.9 days ± 10.5 days with ofloxacin/cefotaxime. The drug-related adverse events were reported in 10.3% of patients on levofloxacin and 8.0% with ofloxacin/cefotaxime (P=0.42). Five patients on levofloxacin and 4 taking ofloxacin/cefotaxime withdrew due to a drug-related adverse event (P=0.75).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or Legionella species.				
Tanaseanu et al.[82] (2008) Levofloxacin 500 mg IV once or twice daily vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV twice daily Patients were allowed to switch to oral levofloxacin after 3 days if specific criteria were met.	RCT, DB, MC Patients >18 years of age hospitalized with community-acquired pneumonia	N=891 7-14 days	Primary: Clinical response in clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) populations at test-of-cure (TOC) Secondary: Health care resource utilization, safety	Primary: At the TOC assessment in the CE and c-mITT populations, there were no significant differences in the clinical cure rates for tigecycline (TGC) as compared with levofloxacin (LEV). Tigecycline cured 89.7% of patients and levofloxacin cured 86.3% of patients (95% CI, -2.2 to 9.1, P<0.001 for non-inferiority). In the study in which patients were allowed to switch to oral levofloxacin therapy after ≥3 days of IV administration of either study medication, there were no significant differences in the percentage of CE patients who switched to oral therapy (TGC, 89.9 %; LEV, 87.8%) or in the median duration of oral therapy in either group (3.9 days for TGC vs 3.32 for LEV). In the c-mITT population, tigecycline 81% of patients and levofloxacin cured 79.7% of patients (95% CI -4.5 to 7.1, P<0.001 for non-inferiority). Secondary: In the pooled studies, there was no significant difference between the 2 treatment groups in hospital LOS during the primary hospitalization (TGC: mean [SD]=9.8 [6.0] days; LEV=9.8 [6.0] days; P=0.883). There was no difference in mean duration of study antibiotic therapy (TGC=9.8 [3.1] days; LEV=10.0 [3.2] days; P=0.453). There were no significant differences between the treatment groups in the rate of rehospitalization, admission for ICU care, admission to emergency room care, use of home health care, or nursing home admissions after discharge from the primary hospitalization. More TGC-treated patients than LEV-treated patients reported that adverse events were considered drug related, and nausea and vomiting occurred at a significantly higher rate for TGC vs LEV (P<0.001). Elevated serum ALT/AST levels occurred at significantly higher rates (P<0.01) for LEV patients compared with TGC patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Discontinuations for adverse events were low (TGC 6.1% and LEV 8.1%).
Tanaseanu et al.[76] (2009) Levofloxacin 500 mg IV QD or BID vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours (TGC)	DB, RCT, MC Patients ≥18 years of age with a community-acquired pneumonia (CAP)	N=428 7 to 14 days	Primary: Clinical response in the clinically evaluable (CE) population and clinical modified ITT (c-mITT) populations at the test of cure (TOC) visit (10 to 21 posttreatment) Secondary: Microbiologic eradication rates	Primary: In the CE population, clinical cure rates at the TOC visit were 88.9% for TGC and 85.3% for levofloxacin (P=0.4025). In the c-mITT population, clinical cure rates were 83.7% for TGC and 81.5% for levofloxacin (P<0.6269). TGC was found to be non-inferior to levofloxacin (P<0.001). Secondary: In the microbiologically evaluable (ME) population, eradication rates at the TOC visit were similar among the treatment groups for common pathogens. The most common isolate was *S. pneumoniae*, with similar eradication for TGC (92%) and levofloxacin (89%). Both therapies eradicated 100% of penicillin-intermediate and penicillin-resistant strains. *M. pneumoniae* was the most commonly identified atypical organism, and was eradicated in 96% of TGC patients and 92% of levofloxacin patients. No obvious differences in eradication rates of other organisms were found, though the number of other isolates was small.
Torres et al.[57] (2008) Moxifloxacin 400 mg IV/PO once daily for 7-14 days vs ceftriaxone 2 g once daily plus levofloxacin 500 mg IV/PO twice daily for 7-14 days	RCT, MC, DB Hospitalized patients with community-acquired pneumonia	N=733 21-28 days posttreatment	Primary: Clinical and bacteriological response at test-of-cure Secondary: Adverse events	Primary: The overall clinical cure rates at test-of-cure were 86.9% for moxifloxacin and 89.9% for the comparator regimen (95% CI, -8.1% to 2.2%). Clinical improvement occurred in 91.8% of patients in the moxifloxacin arm and 93.5% of patients in the comparator arm (95% CI, -5.8 to 2.8) at the during therapy assessment. At follow-up (21-28 days following treatment), cure was maintained in 96% of patients in the moxifloxacin arm and 97.2% of those in the comparator arm (95% CI, -2.8 to 1.1). There was no significant difference in 30-day mortality between the two treatment groups (4.9% vs 3.3% of patients died in the moxifloxacin group compared to the combination treatment group). Bacteriological success at test-of-cure was 83.3% for moxifloxacin and 85.1% for the comparator regimen (95% CI, -15.4% to 11.8%). Secondary: There were no significant differences between moxifloxacin and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				comparator treatments in the frequency of adverse events, premature discontinuation of therapy, or duration of hospitalization.
Shorr et al.[45] (2001) Quinolones (ciprofloxacin 300-400 mg TID or levofloxacin 750 mg QD) vs comparator antibiotics (imipenem-cilastatin or ceftazidime)	MA Patients with nosocomial pneumonia	N=1,186 (5 trials) Variable duration	Primary: Clinical cure rates Secondary: Mortality and eradication rates	Primary: Overall, the odds ratio for clinical cure rates slightly favored quinolones over the comparator treatment (OR=1.12, 95% CI, 0.80 to 1.55). Secondary: Overall mortality rates were 17.2% to 20.9% with quinolones compared with 11.8% to 18.8% with the comparator treatments (OR=0.87, 95% CI, 0.57 to 1.37). Eradication rates observed were 66.4% with quinolones and 57.3% with the comparator treatments (OR=1.41, 95% CI, 1.00 to 2.00).
Salkind et al.[46] (2002) Quinolones (gatifloxacin, moxifloxacin, sparfloxacin, trovafloxacin, or grepafloxacin) vs macrolides, β-lactams or doxycycline	MA Patients with community-acquired pneumonia	N=5,118 (13 trials) Variable duration	Primary: Clinical success rates, defined as resolution or improvement of symptoms	Primary: Summary estimates significantly favor quinolones to the comparator agent in both the intention-to-treat population (OR=1.22, 95% CI, 1.02 to 1.47; P=0.03) and the evaluable population (OR=1.37, 95% CI, 1.11 to 1.68; P=0.003). The number needed to treat for a quinolone advantage was 33 (95% CI, 17 to 362) in the intention-to-treat population and the 37 (95% CI, 22 to 121) in evaluable population.
Miscellaneous Infections				
Metallidis et al.[51] (2008)	RCT	N=95	Primary: Microbiologically	Primary: The overall incidence of microbiologically and clinically documented

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ciprofloxacin 400 mg IV twice daily plus ceftriaxone 4 g IV every 24 hours vs ceftazidime 2 g IV every 8 hours plus amikacin 500 mg IV every 8 hours or 20 mg/kg divided in three doses	Patients with febrile neutropenia	≥3 days	and clinically documented infections	infections was 81.3% (80.85% in the ceftriaxone-ciprofloxacin group and 82.14% in the ceftazidime-amikacin group). There was no significant difference between the groups. The overall incidence of documented infections was 45.9% (51.1% in the ceftriaxone-ciprofloxacin group and 37% in the ceftazidime-amikacin group; P=0.011). The ceftriaxone-ciprofloxacin group had an overall incidence of resolution and improvement of 95.7% in comparison to 75% in the ceftazidime-amikacin group. Thirty-nine organisms were isolated, 66.67% gram-negative and 33.33% gram-positive.
Keramat et al.[77] (2009) Ciprofloxacin 15 mg/kg BID plus rifampin 15 mg/kg QD (CR group) vs ciprofloxacin 15 mg/kg BID plus doxycycline 200 mg QD (CD group) vs doxycycline 200 mg PO QD plus rifampin 15 mg/kg QD (DR group)	PRO, RCT Patients ≥18 years of age with acute brucellosis	N=178 8 to 12 weeks	Primary: Response and relapse rates	Primary: Response to therapy was observed in 93.7% of patients at the end of treatment for all 3 groups (DR 96.7%, CR 95.2%, CD 87.3%). There were no significant differences among the treatment groups (P=0.09). Therapeutic failure was seen in 12 cases, though no significant differences were noted among the 3 groups (P=0.88). After 6 months, 12 patients relapsed (DR 7.7%, CR 8.3%, CD 17.5%; P=0.35).
GIMEMA Infection Program[49]	RCT, MC, SB	N=801	Primary: Number of patients	Primary: Significantly less patients on ciprofloxacin (34%) developed fevers than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1991) Ciprofloxacin 500 mg BID vs norfloxacin 400 mg BID	Patients ≥14 years old with neutropenia with hematologic malignancies or had bone marrow transplantation or chemotherapy-induced neutropenia expected to last >10 days	Mean 29 days	with febrile episodes, the number of days with a fever, the number of days parenteral antibiotics were used, interval to first febrile episode or infection, compliance, classification of febrile episodes or infection, discontinuation due to adverse reactions and mortality	norfloxacin 25% (P=0.01). The number of days with a fever did not differ significantly between treatment groups. Mean duration of parenteral antibiotic use was significantly shorter with ciprofloxacin (10.1 days) vs norfloxacin (12.0 days, P=0.02). The interval to first febrile episode was longer with ciprofloxacin (8.3 days) compared to norfloxacin (7.2 days; P=0.055). Patients with ciprofloxacin had a lower rate of microbiologically documented infections (17% vs 24%; P=0.058). Differences among other febrile classifications (clinically documented infection, fever of unknown origin, or bacteremia) were not significant. Compliance was >90% and comparable between treatment groups. Discontinuation due to adverse events occurred in 2% of patients on norfloxacin and 4% of patients on ciprofloxacin. The mortality rate during neutropenic episodes was 13% with norfloxacin and 14% with ciprofloxacin.
Arjyal et al.[79] (2011) Gatifloxacin 10 mg/kg once daily for 7 days vs chloramphenicol 75 mg/kg/day in four divided doses for 14 days	RCT, OL Patients with uncomplicated enteric fever	N=853 6 months	Primary: Treatment failure Secondary: Fever clearance time, late relapse, and fecal carriage	Primary: There were 14 treatment failures in the chloramphenicol group and 12 treatment failures in the gatifloxacin group (HR 0.86; 95% CI, 0.40 to 1.86; P=0.70). Secondary: The median time to fever clearance was 3.95 days in the chloramphenicol group and 3.90 in the gatifloxacin group (P=0.64). There was no significant difference between the treatment groups in relapses until day 31 (P=0.35) or day 62 (P=0.77). Only three of 148 patients receiving chloramphenicol and none of 154 patients receiving gatifloxacin were stool-culture-positive at the end of 1

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				month (P=0.12). At the end of 3 months, only one patient in the chloramphenicol group had a positive stool culture, and at 6 months no patients had a positive stool culture. In the chloramphenicol group, 25% of culture-positive patients experienced at least one adverse event. In the gatifloxacin group, 16.9% of culture-positive patients experienced at least one adverse event.
Timmers et al.[54] (2007) Levofloxacin 500 mg once daily vs ciprofloxacin 500 mg twice daily plus phenethicillin 250 mg four times daily	RCT, OL Adult patients at high risk for neutropenia who were scheduled to receive intensive treatment for hematological malignancies	N=242 Duration not specified	Primary: Success or failure of the prophylactic regimen Secondary: Time to primary endpoint, occurrence of fever, type and number of infections, use of antimicrobial agents, and tolerance	Primary: Failure of prophylaxis was observed in 73.0% of levofloxacin recipients and in 70.8% of ciprofloxacin plus phenethicillin recipients (RR 1.03, 95% CI 0.88-1.21, P=0.71). Secondary: No differences were noted between the two groups with respect to time to endpoint, occurrence of fever, type and number of microbiologically documented infections, and administration of intravenous antibiotics. The mean tolerance score per day was significantly lower for ciprofloxacin–phenethicillin recipients than for patients receiving levofloxacin (P<0.05). Surveillance cultures indicated the emergence of viridans group streptococci resistant to levofloxacin in 14% of levofloxacin recipients.
Solomkin et al.[73] (2009) Moxifloxacin 400 mg IV once daily for 3 to 14 days vs ceftriaxone 2 g IV once daily plus metronidazole 500 mg IV twice daily for 3 to 14 days	RCT, DB, MC Patients ≥18 years of age with community-origin complicated intra-abdominal infections (cIAIs) with an expected duration of treatment with IV antimicrobials of 3-14 days	N=364 Up to 28 days	Primary: Clinical success rate at the test-of-cure (TOC) visit (10 to 14 days after the end of therapy) Secondary: Clinical and bacteriological success rates on days 3 and 5 during treatment and at the end-of-	Primary: At the TOC visit, cure rates were 90.2% for moxifloxacin and 96.5% for ceftriaxone/metronidazole (95% CI, −11.7 to −1.7). In the ITT population, the clinical cure rates were 87.2% for moxifloxacin and 91.2% for ceftriaxone/metronidazole (95% CI, −10.7 to 1.9). Moxifloxacin was found to be non-inferior to ceftriaxone/metronidazole in the PP and ITT populations. Secondary: During treatment, clinical improvement occurred in similar proportions of PP patients in the moxifloxacin group (31.0%) and the ceftriaxone/metronidazole group (28.1%). In the ITT population, clinical improvement occurred in 30.6% of patients receiving moxifloxacin and 27.1% of patients receiving ceftriaxone/metronidazole.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			therapy (EOT); bacteriological success rate at the TOC visit; and clinical success rate at the TOC visit in patients with bacteriologically proven cIAI	In the per protocol population, clinical resolution at EOT occurred in 92.5% of patients receiving moxifloxacin and in 97.1% of patients receiving ceftriaxone/metronidazole (95% CI, −9.8 to −0.2). In the ITT population, clinical resolution at EOT occurred in 91.1% of patients receiving moxifloxacin and in 94.5% of patients receiving ceftriaxone/metronidazole. Bacteriological success rates were comparable between treatment groups. The bacteriological success rates in the MBV population at TOC support the clinical results of moxifloxacin vs ceftriaxone/metronidazole (89.4% vs 95.9%, respectively; 95% CI, −13.3 to −0.6). The overall incidence of treatment-emergent AEs was similar between the two treatment groups (31.7% with moxifloxacin vs 24.3% with ceftriaxone/metronidazole; P=0.129).
Gupta et al.[74] (2009) Ofloxacin 7.5 mg/kg orally every 12 hours and amoxicillin-clavulanate 12.5 mg/kg orally every 8 hours as outpatient therapy vs ceftriaxone 75 mg/kg/day IV and amikacin 15 mg/kg once daily as outpatient therapy	RCT, SC, OL Pediatric patients 2 to 15 years of age with low-risk febrile neutropenia (LRFN)	N=88 (123 febrile episodes) Variable duration	Primary: Treatment success	Primary: In the per protocol analysis, treatment was successful in 90.16% of episodes in the oral group and in 93.10% of episodes in the intravenous group. In the ITT analysis, the success rate was 88.7% in the oral group and 88.5% in the intravenous group (P=0.97). There were 3 hospitalizations (all in the oral group) and no mortality.
Thaver et al.[50] (2005)	MA	33 trials	Primary: Clinical failure,	Primary: Quinolones significantly reduced clinically diagnosed relapses (OR=0.14,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Quinolones vs comparator antibiotics (chloramphenicol, ceftriaxone, cefixime, azithromycin, and SMX-TMP)	Patients with typhoid and paratyphoid fever	Variable duration	microbiological failure and relapse	95% CI, 0.04 to 0.50) compared to chloramphenicol; however, this was not significant in blood-cultured confirmed relapse. For all other comparisons with chloramphenicol, there were no significant differences. In adults, quinolones significantly reduced clinical failure (OR=0.08, 95% CI, 0.01 to 0.45) compared to ceftriaxone. For all other comparisons with ceftriaxone (microbiologic failure or relapse), there were no significant differences.

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily, PRN=as needed
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PM=post marketing, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=rate ratio, SB=single-blind, TB=triple-blind, XO=crossover

Additional Evidence

Dose Simplification
Three clinical trials directly compared ciprofloxacin extended-release tablets (dosed once daily) with the immediate-release formulation (dosed twice daily). Fourcroy et al. and Henry et al. evaluated women with uncomplicated urinary tract infections receiving treatment for three days.[30,32] Talan et al. evaluated men and women with complicated urinary tract infections or uncomplicated pyelonephritis receiving treatment for 7 to 14 days.[31] In all three trials, patients receiving the extended-release formulation demonstrated similar clinical cure rates, bacteriological eradication rates, and adverse event rates compared to patients receiving the immediate-release formulation.[30-32]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 11. Relative Cost of the Quinolones

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Ciprofloxacin	injection, extended-release tablet, suspension, tablet	Cipro®*, Cipro IV®*, Cipro XR®*, Proquin XR®	$$$$-$$$$$	$-$$$
Gemifloxacin	tablet	Factive®	$$$$	N/A
Levofloxacin	injection, solution, tablet	Levaquin®*	$$$$-$$$$$	$-$$$$
Moxifloxacin	injection, tablet	Avelox®, Avelox ABC Pack®, Avelox IV®	$$$$	N/A
Norfloxacin	tablet	Noroxin®	$$$-$$$$	N/A
Ofloxacin	tablet	N/A	N/A	$$$-$$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The quinolones are approved to treat a variety of infections, including dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-11] Ciprofloxacin, levofloxacin and ofloxacin are available in a generic formulation.

There are many guidelines that define the appropriate place in therapy for the quinolones. The specific agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the quinolone. The quinolones are recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, encephalitis, diabetic foot infections, infectious diarrhea, chancroid, urinary tract infections, anthrax, infectious exacerbations of COPD, community-acquired pneumonia, nosocomial pneumonia, intra-abdominal infections, and febrile neutropenia.[15-18,21-23,25-26,28,60-63,85-86,88,90] They are recommended as an alternative treatment option for meningitis, skin and soft-tissue infections and sexually transmitted diseases.[14,16,64,83]

Clinical trials have demonstrated comparable efficacy among the quinolones for the treatment of skin and soft-tissue infections, genitourinary infections, and respiratory tract infections.[29-44,47-48,52-53,57] Data from published studies supports similar safety profiles among the quinolones. There's an increased risk of tendinitis and tendon rupture with the use of quinolones. This risk is further increased in older patients, patients taking corticosteroid drugs, and patients with kidney, heart, or lung transplants.[1] Because of this risk, the use of quinolones has been limited in the pediatric population. The quinolones may also exacerbate muscle weakness in patients with myasthenia gravis.

There is insufficient evidence to support that one brand quinolone is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand quinolones within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand quinolone is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2010. Available from Wolters Kluwer Health, Inc. Accessed September 2011.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2010; September 2011.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed September 2011.
4. Cipro® [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; May 2011.
5. Cipro IV® [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; April 2011.
6. Cipro XR® [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; May 2011.
7. Proquin XR® [package insert]. Menlo Park, CA: Depomed Inc; February 2011.
8. Factive® [package insert]. Cary, NC: Cornerstone Therapeutics, Inc.; February 2011.
9. Levaquin® [package insert]. Raritan, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc.; April 2011.
10. Avelox® [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; February 2011.
11. Noroxin® [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; May 2011.
12. Hooper DC. Fluoroquinolones. In: UpToDate, Calderwood, SB (Ed), UpToDate, Waltham, MA, 2011.
13. Mandell GL, Bennett JE, Dolin R. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 6th ed. Philadelphia, PA, Elsevier ; 2005.
14. Stevens DL, Bisno AL, Chambers HF, Everett ED, et al; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005;41:1373-406.
15. Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, et al; Infectious Diseases Society of America. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis. 2001;32:331-51.
16. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1-110.
17. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 91: Treatment of urinary tract infections in nonpregnant women. Obstet Gynecol 2008;111:785-94.
18. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20.
19. Braman SS. Chronic cough due to chronic bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129 (1 Suppl): 104S-15S.
20. Braman SS. Chronic cough due to acute bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129 (1 Suppl): 95S-103S.
21. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2010. 117 p. Available at: www.goldcopd.com. Accessed October 2011.
22. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-72.
23. Ramsdell J, Narsavage GL, Fink JB; American College of Chest Physicians' Home Care Network Working Group. Management of community-acquired pneumonia in the home: an American College of Chest Physicians clinical position statement. Chest. 2005 May;127(5):1752-63.
24. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011;53:e25-76.
25. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR, Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:e56-93.
26. Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, et al; Working Group on Civilian Biodefense. Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA 2002;287(17):2236-52.

27. Bossi P, Tegnell A, Baka A, Van Loock F, et al.; Task Force on Biological and Chemical Agent Threats, Public Health Directorate, European Commission, Luxembourg. Bichat guidelines for the clinical management of anthrax and bioterrorism-related anthrax. Euro Surveill. 2004;9(12):1-7.
28. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50:133-64.
29. Rafalsky V, Andreeva I, Rjabkova E. Quinolones for uncomplicated acute cystitis in women. Cochrane Database Syst Rev. 2006, Issue 3. Art. No.:CD003597.DOI10.1002/14651858.CD003597.pub2.
30. Fourcroy JL, Berner B, Chiang YK, Cramer M, Rowe L, Shore N. Efficacy and safety of a novel once-daily extended-release ciprofloxacin tablet formulation for treatment of uncomplicated urinary tract infection in women. Antimicrob Agents Chemother. 2005;49(10):4137-43.
31. Talan DA, Klimberg IW, Nicolle LE, Song J, Kowalsky SF, Church DA. Once daily, extended release ciprofloxacin for complicated urinary tract infections and acute uncomplicated pyelonephritis. J Urol. 2004;171(2 Pt 1):734-39.
32. Henry DC Jr, Bettis RB, Riffer E, Haverstock DC, et al. Comparison of once-daily extended-release ciprofloxacin and conventional twice-daily ciprofloxacin for the treatment of uncomplicated urinary tract infection in women. Clin Ther. 2002;24(12):2088-104.
33. Richard GA, Klimberg IN, Fowler CL, Callery-D'Amico S, Kim SS. Levofloxacin versus ciprofloxacin versus lomefloxacin in acute pyelonephritis. Urology. 1998;52(1):51-5.
34. Bundrick W, Heron SP, Ray P, et al. Levofloxacin versus ciprofloxacin in the treatment of chronic bacterial prostatitis: a randomized double-blind multicenter study. Urology. 2003 Sep;62(3):537-41.
35. Arredondo-Garcia JL, Figueroa-Damian R, Rosas A, Jauregui A, et al. Comparison of short-term treatment regimen of ciprofloxacin versus long-term treatment regimens of trimethoprim/sulfamethoxazole or norfloxacin for uncomplicated lower urinary tract infections: a randomized, multicentre, open-label, prospective study. J Antimicrob Chemother. 2004;54(4):840-3.
36. Schaeffer AJ, Anderson RU. Efficacy and tolerability of norfloxacin vs ciprofloxacin in complicated urinary tract infection. Urology. 1992;40(5):446-9.
37. Perea EJ, Aznar J, Herrera A, Mazuecos J, Rodriguez-Pichardo A. Clinical efficacy of new quinolones for therapy of nongonococcal urethritis. Sex Transm Dis. 1989;16(1):7-10.
38. Auquer F, Cordon F, Gorina E, Caballero JC, Adalid C, Batlle J; Urinary Tract Infection Study Group. Single-dose ciprofloxacin versus 3 days of norfloxacin in uncomplicated urinary tract infections in women. Clin Microbiol Infect. 2002;8(1):50-4.
39. Raz R, Naber KG, Raizenberg C, Rohana Y, et al. Ciprofloxacin 250 mg twice daily versus ofloxacin 200 mg twice daily in the treatment of complicated urinary tract infections in women. Eur J Clin Microbiol Infect Dis. 2000;19(5):327-31.
40. McCarty JM, Richard G, Huck W, Tucker RM, et al. A randomized trial of short-course ciprofloxacin, ofloxacin, or trimethoprim/sulfamethoxazole for the treatment of acute urinary tract infection in women. Ciprofloxacin Urinary Tract Infection Group. Am J Med. 1999;106(3):292-9.
41. Ross JD, Cronje HS, Paszkowski T, Rakoczi I, et al. Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: results of a multicentre, double blind, randomised trial. Sex Transm Infect. 2006;82(6):446-51.
42. Anzueto A, Niederman MS, Pearle J, Restrepo MI, et al. Community-Acquired Pneumonia Recovery in the Elderly (CAPRIE): efficacy and safety of moxifloxacin therapy versus that of levofloxacin therapy. Clin Infect Dis. 2006;42(1):73-81.
43. Leroy O, Saux P, Bedos JP, Caulin E. Comparison of levofloxacin and cefotaxime combined with ofloxacin for ICU patients with community-acquired pneumonia who do not require vasopressors. Chest. 2005;128(1):172-83.
44. Sethi S, Fogarty C, Fulambarker A. A randomized, double-blind study comparing 5 days oral gemifloxacin with 7 days oral levofloxacin in patients with acute exacerbation of chronic bronchitis. Respir Med. 2004;98(8):697-707.
45. Shorr AF, Susla GB, Kollef MH. Quinolones for treatment of nosocomial pneumonia: a meta-analysis. Clin Infect Dis. 2005;40 Suppl 2:S115-S122. Stoner BP, Douglas JM Jr, Martin DH, Hook EW 3rd, et al. Single-dose gatifloxacin compared with ofloxacin for the treatment of uncomplicated gonorrhea: a randomized, double-blind, multicenter trial. Sex Transm Dis. 2001;28(3):136-42.
46. Salkind AR, Cuddy PG, Foxworth JW. Fluoroquinolone treatment of community-acquired pneumonia: a meta-analysis. Ann Pharmacother. 2002;36(12):1938-43.

47. Nicodemo AC, Robledo JA, Jasovich A, Neto W. A multicentre, double-blind, randomised study comparing the efficacy and safety of oral levofloxacin versus ciprofloxacin in the treatment of uncomplicated skin and skin structure infections. Int J Clin Pract. 1998;52(2):69-74.
48. Nichols RL, Smith JW, Gentry LO, Gezon J, et al. Multicenter, randomized study comparing levofloxacin and ciprofloxacin for uncomplicated skin and skin structure infections. South Med J. 1997;90(12):1193-200.
49. GIMEMA Infection Program. Prevention of bacterial infection in neutropenic patients with hematologic malignancies. A randomized, multicenter trial comparing norfloxacin with ciprofloxacin. Ann Intern Med. 1991;115(1):7-12.
50. Thaver D, Zaidi AKM, Critchley JA, Azmatullah A, Madni SA, Bhutta ZA. Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD004530.DOI: 10.1002/14651858.CD004530.pub3.
51. Metallidis S, Kollaras P, Giannakakis T, et al. A prospective, controlled, randomized, non-blind, comparative study of the efficacy and safety of a once daily high dose of ceftriaxone plus ciprofloxacin versus thrice daily ceftazidime plus amikacin in empirical therapy for febrile neutropenic patients. Eur J Intern Med 2008;19:619-24.
52. Peterson J, Kaul S, Khashab M, et al. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. Urology 2008;71:17-22.
53. Klausner H, Brown P, Peterson J, et al. A trial of levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg and/or 500 mg twice daily for 10 days in the treatment of acute pyelonephritis. Curr Med Res Opin 2007;23:2637-45.
54. Timmers G, Simoons-Smit A, Leidekker M, et al. Levofloxacin vs ciprofloxacin plus phenethicillin for the prevention of bacterial infections in patients with haematological malignancies. Clin Microbiol Infect 2007;13:497-503.
55. Vardakas K, Siempos I, Grammatikos A, et al. Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. CMAJ 2008;179:1269-77.
56. Karamanis E, Matthaiou D, Moraitis L, et al. Fluoroquinolones versus beta-lactam based regimens for the treatment of osteomyelitis: a meta-analysis of randomized controlled trials. Spine 2008;33:E297-304.
57. Torres A, Garau J, Arvis P, et al. Moxifloxacin monotherapy is effective in hospitalized patients with community-acquired pneumonia: the MOTIV study--a randomized clinical trial. Clin Infect Dis 2008;46:1499-509.
58. Karageorgopoulos D, Giannopoulou K, Grammatikos A, et al. Fluoroquinolones compared with beta-lactam antibiotics for the treatment of acute bacterial sinusitis: a meta-analysis of randomized controlled trials. CMAJ 2008;178:845-54.
59. Imran H, Tleyjeh I, Arndt C, et al. Fluoroquinolone prophylaxis in patients with neutropenia: a meta-analysis of randomized placebo-controlled trials. Eur J Clin Microbiol Infect Dis 2008;27:53-63.
60. American Thoracic Society and the Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388–416.
61. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Eur Heart J 2009;30:2369-413.
62. Bonow R, Carabello B, Chatterjee K et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e1-142.
63. Hill DR, Ericsson CD, Pearson RD, Keystone JS, Freedman DO, Kozarsky PE, et al. The practice of travel medicine: Guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006; 43:1499-1539.
64. Tunkel AR, Hartman BJ, Kaplan SL, et al. Infectious Diseases Society of America. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267-84.
65. Noel GJ, Blumer JL, Pichichero ME, et al. A randomized comparative study of levofloxacin versus amoxicillin/clavulanate for treatment of infants and young children with recurrent or persistent acute otitis media. Pediatr Infect Dis J 2008;27:483-9.
66. Kaushik JS, Gupta P, Faridi MM et al. Single dose azithromycin versus ciprofloxacin for cholera in children: a randomized 24 hours controlled trial. Indian Pediatr 2010;47:309-15.

67. Molina-Infante J, Perez-Gallardo B, Fernandez-Bermejo M et al. Clinical trial: clarithromycin vs levofloxacin in first-line triple and sequential regimens for Helicobacter pylori eradication. Aliment Pharmacol Ther 2010;31:1077-84.
68. Boothby M, Page J, Pryor R, et al. A comparison of treatment outcomes for moxifloxacin versus ofloxacin/metronidazole for first-line treatment of uncomplicated non-gonococcal pelvic inflammatory disease. Int J STD AIDS 2010;21:195-7.
69. Heystek M, Ross JD, PID Study Group. A randomized double-blind comparison of moxifloxacin and doxycycline/metronidazole/ciprofloxacin in the treatment of acute, uncomplicated pelvic inflammatory disease. Int J STD AIDS 2009;20:690-5.
70. Judlin P, Liao Q, Liu Z, et al. Efficacy and safety of moxifloxacin in uncomplicated pelvic inflammatory disease: the MONALISA study. BJOG 2010;117:1475-84.
71. Vick-Fragoso R, Hernández-Oliva G, Cruz-Alcázar J, et al. Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections. Infection 2009;37:407-17.
72. Nouira S, Marghli S, Besbes L, et al. Standard versus newer antibacterial agents in the treatment of severe acute exacerbation of chronic obstructive pulmonary disease: a randomized trial of trimethoprim-sulfamethoxazole versus ciprofloxacin. Clin Infect Dis 2010;51:143-9.
73. Solomkin J, Zhao YP, Ma EL, et al. Moxifloxacin is non-inferior to combination therapy with ceftriaxone plus metronidazole in patients with community-origin complicated intra-abdominal infections. Int J Antimicrob Agents 2009;34:439-45.
74. Gupta A, Swaroop C, Agarwala S, et al. Randomized controlled trial comparing oral amoxicillin-clavulanate and ofloxacin with intravenous ceftriaxone and amikacin as outpatient therapy in pediatric low-risk febrile neutropenia. J Pediatr Hematol Oncol 2009;31:635-41.
75. Mokabberi R, Haftbaradaran A, Ravakhah K. Doxycycline vs levofloxacin in the treatment of community-acquired pneumonia. J Clin Pharm Ther 2010;35:195-200.
76. Tanaseanu C, Milutinovic S, Calistru PI, et al. Efficacy and safety of tigecycline versus levofloxacin for community-acquired pneumonia. BMC Pulm Med 2009;9:44.
77. Keramat F, Ranjbar M, Mamani M, et al. A comparative trial of three therapeutic regimens: ciprofloxacin-rifampin, ciprofloxacin-doxycycline and doxycycline-rifampin in the treatment of brucellosis. Trop Doct 2009;39:207-10.
78. Griffin AT, Peyrani P, Wiemken T, et al. Macrolides versus quinolones in Legionella pneumonia: results from the Community-Acquired Pneumonia Organization international study. Int J Tuberc Lung Dis 2010;14:495-9.
79. Arjyal A, Basnyat B, Koirala S, et al. Gatifloxacin versus chloramphenicol for uncomplicated enteric fever: an open-label, randomised, controlled trial. Lancet Infect Dis 2011;11:445-54.
80. Naber KG, Llorens L, Kaniga K, et al. Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for treatment of complicated lower urinary tract infection and pyelonephritis. Antimicrob Agents Chemother 2009;53:3782-92.
81. Redman R, Damiao R, Kotey P, et al. Safety and efficacy of intravenous doripenem for the treatment of complicated urinary tract infections and pyelonephritis. J Chemother 2010;22:384-91.
82. Tanaseanu C, Bergallo C, Teglia O, et al. Integrated results of 2 phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia. Diagn Microbiol Infect Dis 2008;61:329-38.
83. Chaudhuri A, Martinez-Martin P, Kennedy PG, Andrew Seaton R, Portegies P, Bojar M, Steiner I; EFNS Task Force. EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. Eur J Neurol 2008;15:649-59.
84. World Health Organization (WHO). Guidelines for the management of sexually transmitted infections. Available at: http://www.who.int/hiv/pub/sti/en/STIGuidelines2003.pdf. Accessed October 2011.
85. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. Circulation. Jun 2005;111:e394-e434.
86. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, LeFrock JL, Lew DP, Mader JT, Norden C, Tan JS; Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004 Oct 1;39(7):885-910.

87. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52:1-38.
88. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM, Whitley RJ, Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303-27.
89. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis. 2004;38:1706–15.
90. World Gastroenterology Organization (WGO). WGO practice guideline: acute diarrhea. Munich, Germany: World Gastroenterology Organization (WGO); 2008 Mar. 28 p. http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/01_acute_diarrhea.pdf. Accessed December 2011.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Sulfonamides
AHFS Class 081220
February 8, 2012

I. Overview

Sulfadiazine and sulfamethoxazole/trimethoprim are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-6] These agents are bacteriostatic and interfere with bacterial growth by inhibiting the synthesis of dihydrofolic acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Due to synergism, the combination of sulfamethoxazole/trimethoprim is often bactericidal and active against a variety of organisms. Resistance to sulfonamides is widespread and cross-resistance among the various sulfonamides is common.

Sulfasalazine is approved for the treatment of ulcerative colitis and rheumatoid arthritis.[1-3,7-8] It is a prodrug that is metabolized into sulfapyridine and 5-aminosalicyclic acid (5-ASA). It is absorbed from the small intestine and must be formulated as an enteric-coated product to reach the systemic circulation.

The sulfonamides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation. This class was last reviewed in August 2009.

Table 1. Sulfonamides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Sulfadiazine	tablet	N/A	sulfadiazine
Sulfamethoxazole and trimethoprim	injection, suspension, tablet	Bactrim®*, Bactrim DS®*, Septra DS®*	sulfamethoxazole and trimethoprim
Sulfasalazine	delayed-release tablet, tablet	Azulfidine®*	sulfasalazine

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

The sulfonamides have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the sulfonamides that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Sulfonamides[1-6]

Organism	Sulfadiazine	Sulfamethoxazole/Trimethoprim
Gram-Positive Aerobes		
Nocardia species	✔	
Staphylococcus aureus	✔	
Streptococcus pneumoniae		✔
Gram-Negative Aerobes		
Chlamydia trachomatis	✔	
Enterobacter species	✔	✔
Escherichia coli	✔	✔
Haemophilus influenzae	✔	✔
Klebsiella species	✔	✔
Morganella morganii		✔
Proteus mirabilis	✔	✔

Organism	Sulfadiazine	Sulfamethoxazole/Trimethoprim
Proteus vulgaris	✔	✔
Shigella flexneri		✔
Shigella sonnei		✔
Protozoan Parasites		
Plasmodium falciparum	✔	
Toxoplasma gondii	✔	
Miscellaneous Organisms		
Pneumocystis carinii		✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the sulfonamides are summarized in Table 3.

Table 3. Treatment Guidelines Using the Sulfonamides

Clinical Guideline	Recommendation(s)

American College of Cardiology (ACC)/American Heart Association (AHA): **2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease[82] (2008)**	Rheumatic Fever Prophylaxis
	• Primary prevention of rheumatic heart disease:
	  o Penicillin G benzathine IM once or penicillin V orally for 10 days
	  o Erythromycin estolate or erythromycin ethylsuccinate orally for 10 days, or azithromycin orally for 5 days in patients who are allergic to penicillin
	• Secondary prevention of rheumatic fever:
	  o Penicillin G benzathine IM every 4 weeks, or penicillin V orally twice daily, or sulfadiazine orally once daily
	  o Erythromycin orally twice daily for patients who are allergic to penicillin

Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines: Management of Encephalitis[71] (2008)**	Empirical Therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or trimethoprim-sulfamethoxazole is recommended • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; trimethoprim-sulfamethoxazole is an alternative in the penicillin-allergic patient • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered • *Tropheryma whipplei:* ceftriaxone, followed by either trimethoprim-sulfamethoxazole or cefixime, is recommended Rickettsioses and Ehrlichioses • *Anaplasma phagocytophilum:* doxycycline is recommended • *Ehrlichia chaffeensis:* doxycycline is recommended • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as

Clinical Guideline	Recommendation(s)
	pregnancy • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative Protozoa • *Acanthamoeba:* trimethoprim-sulfamethoxazole plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; trimethoprim-sulfamethoxazole alone and pyrimethamine plus either atovaquone, clarithromycin, azithromycin, or dapsone are alternatives • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended

European Federation of Neurological Societies (EFNS): **Guideline on the Management of Community-acquired Bacterial Meningitis[72] (2008)**	Empirical Therapy
	• Ceftriaxone 2 g every 12–24 hours or cefotaxime 2 g every 6–8 hours.
	• Alternative therapy: Meropenem 2 g every 8 hours or chloramphenicol 1 g every 6 hours.
	• If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg.
	• Ampicillin/amoxicillin 2 g every 4 hours if *Listeria* is suspected.
	Pathogen Specific Therapy
	• Penicillin-sensitive pneumococcal meningitis:
	  o Benzyl penicillin 250,000 U/kg/day, ampicillin/amoxicillin 2 g every 4 hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every 6–8 hours
	  o Alternative therapy: meropenem 2 g every 8 hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily
	• Pneumococcus with reduced susceptibility to penicillin or cephalosporins:
	  o Ceftriaxone or cefotaxime plus vancomycin ± rifampicin
	  o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin
	• Meningococcal meningitis:
	  o Benzyl penicillin, ceftriaxone, or cefotaxime
	  o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin
	• *Haemophilus influenzae* type B:

Clinical Guideline	Recommendation(s)
	o Ceftriaxone or cefotaxime o Alternative therapy: chloramphenicol–ampicillin/amoxicillin • Listerial meningitis: o Ampicillin or amoxicillin 2 g every 4 hours ± gentamicin 1–2 mg every 8 hours for the first 7– 10 days o Alternative therapy: trimethoprim–sulfamethoxazole 10–20 mg/kg every 6–12 hours or meropenem • *Staphylococcal* species: o Flucloxacillin 2 g every 4 hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem • Pseudomonal meningitis: o Meropenem ± gentamicin
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Bacterial Meningitis[9] (2004)**	Empiric Therapy • Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative CSF Gram stain result: • Age <1 month: ampicillin plus cefotaxime or ampicillin plus an aminoglycoside • Age 1–23 months: vancomycin plus a third-generation cephalosporin • Age 2-50 years: vancomycin plus a third-generation cephalosporin • Age >50 years: Vancomycin plus ampicillin plus a third-generation cephalosporin • Basilar skull fracture: vancomycin plus a third-generation cephalosporin • Penetrating head trauma: Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem • Postneurosurgery: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem • CSF shunt: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem Specific Therapy • Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility. • *Streptococcus pneumoniae* o Penicillin MIC <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapies include ceftriaxone, cefotaxime, or chloramphenicol o Penicillin MIC 0.1-1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include cefepime or meropenem o Penicillin MIC ≥2 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime; alternative therapies include gatifloxacin or moxifloxacin o Cefotaxime or ceftriaxone MIC ≥1.0 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime (consider addition of rifampin if MIC of ceftriaxone is >2 µg/mL); alternative therapies include gatifloxacin or moxifloxacin • *Neisseria meningitides* o Penicillin MIC <0.1 µg/mL: standard therapy includes

Clinical Guideline	Recommendation(s)
	penicillin G or ampicillin; alternative therapy includes ceftriaxone, cefotaxime or chloramphenicol o Penicillin MIC 0.1- 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include chloramphenicol, a fluoroquinolone or meropenem • *Listeria monocytogenes* o Standard therapy includes ampicillin or penicillin G; alternative therapies include trimethoprim-sulfamethoxazole or meropenem • *Streptococcus agalactiae* o Standard therapy includes ampicillin or penicillin G; alternative therapies include ceftriaxone or cefotaxime • *Escherichia coli* and other enterobacteriaceae o Standard therapy includes a third-generation cephalosporin; alternative therapies include aztreonam, fluoroquinolone, meropenem, trimethoprim-sulfamethoxazole or ampicillin • *Pseudomonas aeruginosa* o Standard therapies include cefepime or ceftazidime; alternative therapies include aztreonam, ciprofloxacin, or meropenem (addition of an aminoglycoside should be considered) • *Haemophilus influenzae* β-lactamase negative strains o Standard therapy includes ampicillin; alternative therapies include ceftriaxone, cefotaxime, cefepime, chloramphenicol or a fluoroquinolone • *Haemophilus influenzae* β-lactamase positive strains o Standard therapy includes a third-generation cephalosporin; alternative therapies include cefepime, chloramphenicol or a fluoroquinolone • *Staphylococcus aureus* methicillin susceptible o Standard therapy includes nafcillin or ofloxacin; alternative therapies include vancomycin or meropenem • *Staphylococcus aureus* methicillin resistant o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapies include trimethoprim-sulfamethoxazole or linezolid • *Staphylococcus epidermidis* o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapy includes linezolid • *Enterococcus* species ampicillin susceptible o Standard therapy includes ampicillin plus gentamicin • *Enterococcus* species ampicillin resistant o Standard therapy includes vancomycin plus gentamicin • *Enterococcus* species ampicillin and vancomycin resistant o Standard therapy includes linezolid
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections[73] (2005)**	Overview • Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first- or second-generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of methicillin-resistant S*taphylococcus aureus* (MRSA) strains. Animal Bites • Oral treatment options o Amoxicillin/clavulanate is recommended. o Alternative oral agents include doxycycline, as well as

Clinical Guideline	Recommendation(s)
	penicillin VK plus dicloxacillin. o Other options, including fluoroquinolones, trimethoprim-sulfamethoxazole, and cefuroxime, may require an additional agent active against anaerobes, such as metronidazole or clindamycin. o First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *P. multocida* and should be avoided. • Intravenous treatment options o β-lactam/β-lactamase combinations, piperacillin/tazobactam, second-generation cephalosporins, and carbapenems. o Second-generation and third-generation cephalosporins may be used but may require the addition of an anti-anaerobic agent. <u>Human Bites</u> • Clenched-fist injuries often require hospitalization and intravenous antimicrobial therapy with agents such as cefoxitin, ampicillin/sulbactam, ertapenem, or some combination that covers *S. aureus*, *Haemophilus* species, *E. corrodens,* and β-lactamase–producing anaerobes. • *E. corrodens* is usually resistant to first-generation cephalosporins, macrolides, clindamycin, and aminoglycosides, and these agents should be avoided as monotherapy. • In the type 1 β-lactam–allergic patient, fluoroquinolones plus clindamycin, or trimethoprim-sulfamethoxazole plus metronidazole may be useful.
Infectious Diseases Society of America (IDSA): **Diagnosis and Treatment of Diabetic Foot Infections**[74] **(2004)**	• Empirical antibiotic regimens should be based on the clinical severity of the infection. • Current clinical data does not allow for the recommendation of any specific antibiotic regimen for diabetic foot infections (DFIs). • Suggested agents are derived from available published clinical trials and expert experience. • Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have US Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid is currently specifically approved for diabetic foot infections. • Suggested empirical antibiotic regimens for mild infections: dicloxacillin, clindamycin, cephalexin, trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, levofloxacin • Suggested empirical antibiotic regimens for moderate infections: trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, levofloxacin, cefoxitin, ceftriaxone, ampicillin/sulbactam, linezolid (with or without aztreonam), daptomycin (with or without aztreonam), ertapenem, cefuroxime (with or without metronidazole), ticarcillin/clavulanate, piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin • Suggested empirical antibiotic regimens for severe infections: piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin, imipenem-cilastatin, vancomycin and ceftazidime (with or without metronidazole)
World Gastroenterology Organization (WGO): **Acute**	<u>General Considerations</u> • Antimicrobials are the drugs of choice for empirical treatment of

Clinical Guideline	Recommendation(s)

Diarrhea[70] (2008)	traveler's diarrhea and of community-acquired secretory diarrhea when the pathogen is known.
	• Consider antimicrobial treatment for:
	  o Persistent *Shigella*, *Salmonella*, *Campylobacter*, or parasitic infections
	  o Infections in the aged, immunocompromised patients, and patients with impaired resistance, sepsis, or with prostheses
	  o Moderate/severe traveler's diarrhea or diarrhea with fever and/or with bloody stools (quinolones as initial therapy or co-trimoxazole as a second choice)
	• Nitazoxanide may be appropriate for *Cryptosporidium* and other infections, including some bacteria.
	• Rifaximin may also be useful.
	<u>Antimicrobial Agents for the Treatment of Specific Causes of Diarrhea</u>
	• Cholera
	  o First-line: doxycycline or tetracycline
	  o Alternative: azithromycin or ciprofloxacin
	• Shigellosis
	  o First-line: ciprofloxacin
	  o Alternative: pivmecillinam or ceftriaxone
	• Amebiasis
	  o First-line: metronidazole
	• Giardiasis
	  o First-line: metronidazole
	• *Campylobacter*
	  o First-line: azithromycin

Infectious Diseases Society of America (IDSA): **The Practice of Travel Medicine[11] (2006)**	<u>Chemoprophylaxis</u> • Bismuth subsalicylate–containing formulations and antibiotics have been proven effective in preventing traveler's diarrhea. • Probiotics, such as lactobacillus, have not demonstrated sufficient efficacy to be recommended. • Widespread drug resistance renders doxycycline and trimethoprim-sulfamethoxazole (TMP-SMX) no longer useful for prevention of traveler's diarrhea. • Chemoprophylaxis can contribute to development of resistant enteric bacteria and potentially predispose the traveler to infection with other deleterious pathogens, such as *Clostridium difficile.* • The routine use of antibiotic prophylaxis for travelers' diarrhea is not generally recommended. • Chemoprophylaxis may be considered in healthy travelers for whom staying well is critical and in special-needs travelers in whom the risk for diarrhea is increased or the consequences of a diarrheal episode may be severe. • When considering chemoprophylaxis, fluoroquinolone antibiotics remain the first choice. • Chemoprophylaxis should be recommended for no more than 2–3 weeks. <u>Treatment</u> • Fluid replacement and a diet restricted to liquids and bland foods may be appropriate, though they may not provide additional benefits beyond antibiotic treatment. • Symptomatic therapy with bismuth subsalicylate may be recommended in mild cases of diarrhea, but better agents exist for moderate-to-severe disease.

Clinical Guideline	Recommendation(s)
	• Loperamide has become the antimotility agent of choice. It is more efficacious in controlling diarrhea than bismuth subsalicylate and has an onset of action within the first 4 hours after ingestion. When it is used in combination with an antibiotic, there may be rapid improvement of traveler's diarrhea. • Antibiotics are effective in the treatment of traveler's diarrhea and can reduce the average duration of disease from several days to ~1 day. • Antibiotics that are recommended include fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin, levofloxacin), azithromycin, and rifaximin. • Fluoroquinolones remain predictably active for empiric therapy in most parts of the world and remain the drugs of first choice. • Antibiotics that are no longer recommended because of drug resistance worldwide are the sulfonamides, neomycin, ampicillin, doxycycline, tetracycline, trimethoprim alone, and TMP-SMX.

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Infectious Diarrhea[75] (2001)**	<u>Recommendations for Therapy Against Specific Pathogens</u>
	• *Shigella* species:
	  o Trimethoprim-sulfamethoxazole (TMP-SMZ)
	  o Fluoroquinolone
	  o Nalidixic acid
	  o Ceftriaxone
	  o Azithromycin
	• *Salmonella,* non-typhi species:
	  o Treatment is not routinely recommended; however, consider therapy in patients <6 months old or >50 years old, or patients that have a prosthesis, valvular heart disease, severe atherosclerosis, malignancy, or uremia.
	  o TMP-SMZ
	  o Fluoroquinolone
	• *Campylobacter* species
	  o Erythromycin
	• *Escherichia coli* species
	  o TMP-SMZ
	  o Fluoroquinolone
	• *Aeromonas* or *Plesiomonas* species
	  o TMP-SMZ
	  o Fluoroquinolone
	• *Yersinia* species
	  o Antibiotic therapy is not usually required. For severe infections or associated bacteremia, combination therapy with doxycycline, aminoglycosides TMP-SMZ or a fluoroquinolone is recommended.
	• *Vibrio cholerae*
	  o Doxycycline or tetracycline
	  o Fluoroquinolone
	• Toxigenic *Clostridium difficile*
	  o Metronidazole
	• *Isospora* species
	  o TMP-SMZ
	• *Cyclospora* species
	  o TMP-SMZ

American College of Gastroenterology (ACG): **Ulcerative Colitis Practice Guidelines in Adults[10]**	<u>Recommendations for Management of Mild-Moderate Distal Colitis</u> • Patients with mild to moderate distal colitis may be treated with oral aminosalicylates, topical mesalamine, or topical steroids. • Topical mesalamine agents are more effective than topical steroids or

Clinical Guideline	Recommendation(s)
(2010)	oral aminosalicylates. • The combination of oral and topical aminosalicylates is more effective than either alone. • In patients refractory to oral aminosalicylates or topical corticosteroids, mesalamine enemas or suppositories may still be effective. • The unusual patient who is refractory to all of the above agents in maximal doses, or who is systemically ill, may require treatment with oral prednisone in doses up to 40– 60 mg per day, or infliximab with an induction regimen of 5 mg/kg at weeks 0, 2, and 6, although the latter two agents have not been studied specifically in patients with distal disease. <u>Recommendations for Maintenance of Remission in Distal Disease</u> • Mesalamine suppositories are effective in the maintenance of remission in patients with proctitis, whereas mesalamine enemas are effective in patients with distal colitis when dosed even as infrequently as every third night. • Sulfasalazine, mesalamine compounds, and balsalazide are also effective in maintaining remission; the combination of oral and topical mesalamine is more effective than either one alone. • Topical corticosteroids have not proven effective for maintaining remission in distal colitis. • When all of these measures fail to maintain remission in distal disease, thiopurines (6-mercaptopurine (6-MP) or azathioprine) and infliximab, but not corticosteroids, may prove effective. <u>Recommendations for Management of Mild-Moderate Extensive Colitis: Active Disease</u> • Patients with mild to moderate extensive colitis should begin therapy with oral sulfasalazine in daily doses titrated up to 4 – 6 g per day, or an alternate aminosalicylate in doses up to 4.8 g per day of the active 5-aminosalicylate acid (5-ASA) moiety. • Oral steroids are generally reserved for patients who are refractory to oral aminosalicylates in combination with topical therapy, or for patients whose symptoms are so troubling as to demand rapid improvement. • 6-MP and azathioprine are effective for patients who do not respond to oral steroids, and continue to have moderate disease, and are not so acutely ill as to require intravenous therapy. • Infliximab is an effective treatment for patients who are steroid refractory or steroid dependent despite adequate doses of a thiopurine, or who are intolerant of these medications. The infliximab induction dose is 5 mg/kg intravenously at weeks 0, 2, and 6 weeks. • Infliximab is contraindicated in patients with active infection, untreated latent TB, preexisting demyelinating disorder or optic neuritis, moderate to severe congestive heart failure, or current or recent malignancies. <u>Recommendations for Mild-Moderate Extensive Colitis: Maintenance of Remission</u> • Once the acute attack is controlled, a maintenance regimen is usually required, especially in patients with extensive or relapsing disease. • Sulfasalazine, olsalazine, mesalamine, and balsalazide are all effective in reducing relapses. • Patients should not be treated chronically with steroids. Azathioprine or 6-MP may be useful as steroid-sparing agents for steroid-dependent patients and for maintenance of remission not adequately sustained by aminosalicylates, and occasionally for patients who are steroid

Clinical Guideline	Recommendation(s)
	dependent but not acutely ill. • Infliximab is effective in maintaining improvement and remission in the patients responding to the infliximab induction regimen. Recommendations for Management of Severe Colitis • The patient with severe colitis refractory to maximal oral treatment with prednisone, oral aminosalicylate drugs, and topical medications may be treated with infliximab 5 mg/kg if urgent hospitalization is not necessary. • The patient who presents with toxicity should be admitted to hospital for a course of intravenous steroids. • Failure to show significant improvement within 3 – 5 days is an indication for either colectomy or treatment with intravenous cyclosporine in the patient with severe colitis. • Long-term remission in these patients is significantly enhanced with the addition of maintenance 6-MP. • Infliximab may also be effective in avoiding colectomy in patients failing intravenous steroids but its long-term efficacy is unknown in this setting.

Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines[12] (2010)**	Granuloma Inguinale (Donovanosis)
	• Recommended regimen:
	  o Doxycycline 100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed
	• Alternative regimens:
	  o Azithromycin 1 g orally once per week for at least 3 weeks and until all lesions have completely healed
	  o Ciprofloxacin 750 mg orally twice a day for at least 3 weeks and until all lesions have completely healed
	  o Erythromycin base 500 mg orally four times a day for at least 3 weeks and until all lesions have completely healed
	  o Trimethoprim-sulfamethoxazole one double-strength (160 mg/800 mg) tablet orally twice a day for at least 3 weeks and until all lesions have completely healed
	• The addition of an aminoglycoside (e.g., gentamicin 1 mg/kg IV every 8 hours) to these regimens can be considered if improvement is not evident within the first few days of therapy.

Infectious Diseases Society of America (IDSA)/European Society for Microbiology and Infectious Diseases (ESCMID): **International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women[14] (2010)**	Acute Uncomplicated Bacterial Cystitis • Nitrofurantoin monohydrate/macrocrystals (100 mg BID for 5 days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage. • Trimethoprim-sulfamethoxazole (160/800 mg BID for 3 days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible. • Fosfomycin (3 g in a single dose) is an appropriate choice for therapy where it's available due to minimal resistance and propensity for collateral damage, but it appears to be less effective compared to standard short-course regimens. • Ofloxacin, ciprofloxacin and levofloxacin are highly efficacious in 3-day regimens, but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis. • β-lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in 3-7 day regimens are appropriate choices for therapy when other recommended agents cannot be used. Other β-

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	lactams, such as cephalexin are less well studied, but may also be appropriate in certain settings. The β-lactams are generally less effective and have more adverse effects compared with other UTI antimicrobials. For these reasons, β-lactams should be used with caution for uncomplicated cystitis. • Amoxicillin or ampicillin should not be used for empirical treatment given the relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. Acute Pyelonephritis • Oral ciprofloxacin (500 mg BID) for 7 days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice when resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. A long-acting antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) may replace the initial one time IV ciprofloxacin, and is recommended if the fluoroquinolone resistance is thought to exceed 10%. • Once-daily fluoroquinolones (ciprofloxacin 100 mg extended-release for 7 days, levofloxacin 750 mg for 5 days) is an appropriate choice when resistance to community uropathogens is not known to exceed 10%. If resistance is thought to exceed 10%, an initial intravenous dose of long-acting parenteral antimicrobial (ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral trimethoprim/sulfamethoxazole (160/800 mg BID) for 14 days is an appropriate choice of therapy when the uropathogen is known to be susceptible. If susceptibility is unknown, an initial IV dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral β-lactams are less effective than other available agents for the treatment of pyelonephritis. If an oral β-lactam is used, an initial IV dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • For patients requiring hospitalization, initial treatment with an intravenous antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin with or without an aminoglycoside, or a carbapenem is recommended. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results.
American College of Obstetricians and Gynecologists (ACOG): **Treatment of Urinary Tract Infections in Nonpregnant Women[13] (2008)**	• For uncomplicated acute bacterial cystitis, recommended treatment regimens are as follows: o Trimethoprim–sulfamethoxazole: 1 tablet (160 mg trimethoprim–800 mg sulfamethoxazole) twice daily for 3 days. o Trimethoprim 100 mg twice daily for 3 days. o Ciprofloxacin 250 mg twice daily for 3 days, levofloxacin 250 mg once daily for 3 days, norfloxacin 400 mg twice daily for 3 days, or gatifloxacin 200 mg, once daily for 3 days. o Nitrofurantoin macrocrystals 50 to 100 mg 4 times daily for 7 days, or nitrofurantoin monohydrate 100 mg twice daily for 7 days. o Fosfomycin tromethamine, 3-g dose (powder) single dose.
American Academy of Pediatrics (AAP)/American Academy of Family Physicians (AAFP): **Diagnosis and Management of Acute Otitis Media[18]**	Observation Option • Observation without use of antibacterial agents in a child with uncomplicated acute otitis media (AOM) is an option for selected children based on diagnostic certainty, age, illness severity, and

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(2004)	assurance of follow-up. The "observation option" for AOM refers to deferring antibacterial treatment of selected children for 48 to 72 hours and limiting management to symptomatic relief. This option should be limited to otherwise healthy children 6 months to 2 years of age with non-severe illness at presentation and an uncertain diagnosis and to children 2 years of age and older without severe symptoms at presentation or with an uncertain diagnosis. Antibacterial Options - Temperature <39°C Without Severe Otalgia • For the initial treatment of otitis media, the recommended agent is amoxicillin 80-90 mg/kg/day. • For treatment failures at 48-72 hours after initial management with observation option, the recommended agent is amoxicillin 80-90 mg/kg/day. • For treatment failures at 48-72 hours after initial management with antibacterial agents, the recommended agent is amoxicillin-clavulanate. Antibacterial Options - Temperature ≥39°C and/or Severe Otalgia • For the initial treatment of otitis media, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48-72 hours after initial management with observation option, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48-72 hours after initial management with antibacterial agents, the recommended agent is ceftriaxone for 3 days.
American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI): **Diagnosis and Management of Sinusitis: An Updated Practice Parameter**[76] **(2005)**	• Antibiotics are the primary therapy for bacterial sinusitis. • The most common bacteria observed in acute sinusitis, recurrent acute sinusitis, and acute exacerbations of chronic sinusitis are *S pneumoniae*, *H influenzae*, and *M catarrhalis*. • Choice of antibiotic should be based on predicted effectiveness and side effects. • Amoxicillin is a reasonable initial antibiotic choice in both children and adults with uncomplicated disease. • Trimethoprim-sulfamethoxazole can be used as an alternative drug in adults. Resistance is more commonly seen in children, and it is recommended that the clinician refer to their local biogram profile of antibiotic resistance. • For patients allergic to or intolerant of amoxicillin, alternatives include cephalosporins, macrolides, or quinolones. • First-generation cephalosporins, such as cephalexin and cefadroxil, have the disadvantage of poor coverage for *H influenzae* and are therefore inappropriate. • Cefaclor has inadequate activity against all β-lactamase–producing *M catarrhalis* and some, but not all, *H influenzae*. The high prevalence of serum sickness–like reactions makes it an unattractive candidate for treatment. • Other second-generation cephalosporins are cefuroxime axetil and cefprozil. These drugs have the advantage of twice-daily administration and significantly enhanced activity against β-lactamase–producing *H influenzae*, *M catarrhalis*, and *S aureus*. • Cefixime, ceftibuten, cefpodoxime axetil, and cefdinir are third-generation cephalosporins, which can be given orally once or twice daily. Both cefixime and ceftibuten have poor activity against *S pneumoniae* and are especially ineffective against penicillin-resistant strains. Neither of these drugs should be used for acute bacterial sinusitis. Cefpodoxime and cefdinir are suitable agents. • Acute sinusitis generally responds to treatment for 10 to 14 days. Some

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	physicians continue treatment for 7 days after the patient is well to ensure complete eradication of the organism and prevent relapse. • A reasonable approach would be to start the patient on amoxicillin for 3 to 5 days and determine whether the signs and symptoms are improving. If the patients symptoms are improving, continue this treatment until the patient is well for 7 days (generally a 10- to 14-day course). If after 3 to 5 days the patient has not shown improvement, switch to a different antibiotic, such as high-dose amoxicillin-clavulanate or cefuroxime axetil.
American Academy of Pediatrics (AAP): **Clinical Practice Guideline: Management of Sinusitis**[77] **(2001)**	• Antibiotics are recommended for the management of acute bacterial sinusitis to achieve a more rapid clinical cure. • The principle bacterial pathogens in bacterial sinusitis are *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis.* • For children younger than 2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in degree of severity, who do not attend day care, and have not recently been treated with an antimicrobial, amoxicillin is recommended. • If the patient is allergic to amoxicillin, either cefdinir, cefuroxime, or cefpodoxime can be used (only if the allergic reaction was not a type 1 hypersensitivity reaction). • In cases of serious allergic reactions, clarithromycin or azithromycin can be used in an effort to select an antimicrobial of an entirely different class. The Food and Drug Administration has not approved azithromycin for use in patients with sinusitis. • Alternative therapy in the penicillin-allergic patient who is known to be infected with a penicillin-resistant *S pneumoniae* is clindamycin. • If patients do not improve while receiving the usual dose of amoxicillin (45 mg/kg/d), have recently been treated with an antimicrobial, have an illness that is moderate or more severe, or attend day care, therapy should be initiated with high-dose amoxicillin-clavulanate (80–90 mg/kg/d of amoxicillin component, with 6.4 mg/kg/d of clavulanate in 2 divided doses). • Alternative therapies include cefdinir, cefuroxime, or cefpodoxime. A single dose of ceftriaxone, given either intravenously or intramuscularly, can be used in children with vomiting that precludes administration of oral antibiotics. Twenty-four hours later, when the child is clinically improved, an oral antibiotic is substituted to complete the therapy. • Recent pneumococcal surveillance studies indicate that resistance to trimethoprim-sulfamethoxazole and erythromycin-sulfisoxazole is substantial. Therefore, when patients fail to improve while receiving amoxicillin, neither trimethoprim-sulfamethoxazole nor erythromycin-sulfisoxazole are appropriate choices for antimicrobial therapy. • For patients who do not improve with a second course of antibiotics or who are acutely ill, there are 2 options. It is appropriate to consult an otolaryngologist for consideration of maxillary sinus aspiration to obtain a sample of sinus secretions for culture and sensitivity so that therapy can be adjusted precisely. Alternatively, the physician may prescribe intravenous cefotaxime or ceftriaxone (either in hospital or at home) and refer to an otolaryngologist only if the patient does not improve on intravenous antibiotics.
American College of Chest Physicians (ACCP): **Chronic Cough Due to Acute**	• For patients with the putative diagnosis of acute bronchitis, routine treatment with antibiotics is not justified and should not be offered.

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Bronchitis, ACCP Evidence-Based Clinical Practice Guidelines[17] (2006)	
American College of Chest Physicians (ACCP): **Chronic Cough Due to Chronic Bronchitis, ACCP Evidence-Based Clinical Practice Guidelines[16] (2006)**	• In stable patients with chronic bronchitis, there is no role for long-term prophylactic therapy with antibiotics. • In patients with acute exacerbations of chronic bronchitis, the use of antibiotics is recommended; patients with severe exacerbations and those with more severe airflow obstruction at baseline are the most likely to benefit.

Global Initiative for Chronic Obstructive Lung Disease (GOLD): **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[15] (2010)**	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in COPD.
	• There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful.
	• Based on current available evidence, antibiotics should be given to:
	  o Patients with exacerbations of COPD with the following three cardinal symptoms: dyspnea, sputum volume, and sputum purulence.
	  o Patients with exacerbations of COPD with two of the cardinal symptoms, if the increased purulence of sputum is one of the two symptoms.
	  o Patients with a severe exacerbation of COPD that requires mechanical ventilation (invasive or noninvasive).
	• Antibiotic treatment in exacerbations of COPD:
	  o Group A (mild exacerbation; no risk factors for poor outcome)
	  ▪ Recommended oral treatment: β-lactam (penicillin, ampicillin, amoxicillin), tetracycline, or trimethoprim-sulfamethoxazole
	  ▪ Alternative oral treatment: β-lactam/β-lactamase inhibitor, macrolides, second or third generation cephalosporin, or ketolides
	  o Group B (moderate exacerbation with risk factor(s) for poor outcome)
	  ▪ Recommended oral treatment: β-lactam/β-lactamase inhibitor
	  ▪ Alternative oral treatment: fluoroquinolones (gemifloxacin, levofloxacin, moxifloxacin)
	  ▪ Parenteral treatment: β-lactam/β-lactamase inhibitor, second or third generation cephalosporin, or fluoroquinolones (levofloxacin, moxifloxacin)
	  o Group C (severe exacerbation with risk factors for *P. aeruginosa* infection)
	  ▪ Recommended oral treatment: fluoroquinolones (ciprofloxacin, levofloxacin)
	  ▪ Parenteral treatment: fluoroquinolones (ciprofloxacin, levofloxacin) or β-lactam with *P. aeruginosa* activity

Center for Disease Control and Prevention (CDC): **Recommended Antimicrobial Agents for the Treatment and Postexposure Prophylaxis of Pertussis[78]**	• Macrolides (erythromycin, clarithromycin, and azithromycin) are preferred for the treatment of pertussis in patients >1 month of age. For infants aged <1 month, azithromycin is preferred; erythromycin and clarithromycin are not recommended. • For treatment of patients >2 months of age, an alternative agent to macrolides is trimethoprim-sulfamethoxazole (TMP–SMZ).

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(2005)	• The choice of antimicrobial should take into account effectiveness, safety, tolerability, and ease of adherence to the regimen. • Azithromycin and clarithromycin are as effective as erythromycin for treatment of pertussis in patients aged >6 months, are better tolerated, and are associated with fewer and milder side effects than erythromycin. • Erythromycin and clarithromycin, but not azithromycin, are inhibitors of the cytochrome P450 enzyme system (CYP3A subclass) and can interact with other drugs that are metabolized by this system. • Azithromycin and clarithromycin are more resistant to gastric acid, achieve higher tissue concentrations, and have a longer half-life than erythromycin, allowing less frequent administration (1–2 doses per day) and shorter treatment regimens (5–7 days).
National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Diseases Society of America (HIVMA/IDSA): **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents**[19] **(2008)**	Primary Prophylaxis of *Pneumocystis (carinii) jiroveci* pneumonia (PCP) • Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily is also effective and might be better tolerated than one double-strength tablet daily. One double-strength tablet three times weekly is also effective. TMP-SMX at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infections. Lower doses of TMP-SMX likely also confer such protection. • For patients who have an adverse reaction that is not life threatening, chemoprophylaxis with TMP-SMX should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting TMP-SMX should be strongly considered after the adverse event has resolved. Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens or reintroduction of TMP-SMX at a reduced dose or frequency; as many as 70% of patients can tolerate such reinstitution of therapy. • Primary PCP prophylaxis should be discontinued for adult and adolescent patients who have responded to ART with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. Treatment of *Pneumocystis (carinii) jiroveci* pneumonia (PCP) • TMP-SMX is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that TMP-SMX is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate. Oral outpatient therapy of TMP-SMX is highly effective among patients with mild-to-moderate disease. • Patients who have PCP despite TMP-SMX prophylaxis are usually effectively treated with standard doses of TMP-SMX. • Patients with documented or suspected PCP and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific PCP therapy. • The recommended duration of therapy for PCP is 21 days. • Patients who have a history of PCP should be administered

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	chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with TMP-SMX unless immune reconstitution occurs as a result of ART. • Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ count has increased from <200 cells/µL to >200 cells/µL for >3 months as a result of ART. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. If PCP recurs at a CD4+ count of ≥200 cells/µL, lifelong prophylaxis should be administered. Primary Prophylaxis of *Toxoplasma* Encephalitis (TE) • The double-strength tablet daily dose of TMP-SMX recommended as the preferred regimen for PCP prophylaxis is effective against TE as well and is therefore recommended. TMP-SMX, one double-strength tablet three times weekly, is an alternative. • If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against PCP. • Atovaquone with or without pyrimethamine/leucovorin can also be considered. • Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against TE and is not recommended. • Prophylaxis against TE should be discontinued among adult and adolescent patients who have responded to ART with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis for TE should be reintroduced if the CD4+ count decreases to <100–200 cells/µL. Treatment of *Toxoplasma* Encephalitis (TE) • The initial therapy of choice for TE consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin. • The preferred alternative regimen for patients with TE who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin. • TMP-SMX was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with TMP-SMX, treatment with this drug may be considered an option. • Acute therapy for TE should be continued for at least 6 weeks, if there is clinical and radiologic improvement.
Infectious Diseases Society of America (IDSA): **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus*[79] (2011)**	Skin and Soft-Tissue Infections (SSTIs) • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired (CA) MRSA is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic

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	streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for CA-MRSA is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of CA-MRSA in outpatients with SSTI, oral antibiotic options include the following: clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and CA-MRSA is desired, options include the following: clindamycin alone or TMP-SMX or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of SSTIs is not recommended. • For hospitalized patients with complicated SSTIs, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for MRSA should be considered pending culture data. Options include the following: vancomycin intravenous (IV), linezolid oral (PO) or IV, daptomycin IV, telavancin IV, and clindamycin IV or PO. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to MRSA-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with cSSTIs, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin IV is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative. <u>MRSA Bacteremia and Infective Endocarditis (Native Valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin IV for at least 2 weeks is recommended. For complicated bacteremia, 4–6 weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, IV vancomycin or daptomycin for 6 weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>MRSA Bacteremia and Infective Endocarditis (Prosthetic Valve)</u> • IV vancomycin plus rifampin PO/IV for at least 6 weeks plus gentamicin IV for 2 weeks. • In children, vancomycin IV is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from 2 to 6 weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin IV may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy

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	with rifampin or gentamicin in children with bacteremia or infective endocarditis.
	Management of MRSA Pneumonia
	• For hospitalized patients with severe community-acquired pneumonia, empirical therapy for MRSA is recommended pending sputum and/or blood culture results.
	• For health care–associated MRSA (HA-MRSA) or CA-MRSA pneumonia, IV vancomycin or linezolid PO/IV or clindamycin PO/IV, if the strain is susceptible, is recommended for 7–21 days, depending on the extent of infection.
	• In children, IV vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin IV can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative.
	Management of MRSA Bone and Joint Infections
	• Antibiotics available for parenteral administration include IV vancomycin and daptomycin.
	• Some antibiotic options with parenteral and oral routes of administration include the following: TMP-SMX in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.
	• A minimum 8-week course is recommended. Some experts suggest an additional 1–3 months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with TMP-SMX, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities.
	• For septic arthritis, refer to antibiotic choices for osteomyelitis. A 3 to 4-week course of therapy is suggested.
	Management of MRSA Infections of the CNS
	• Meningitis
	  o IV vancomycin for 2 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid or TMP-SMX.
	  o For CNS shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid (CSF) cultures are repeatedly negative.
	• Brain abscess, subdural empyema, spinal epidural abscess
	  o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and TMP-SMX.
	• Septic thrombosis of cavernous or dural venous sinus
	  o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and TMP-SMX.
	  o IV vancomycin is recommended in children.

Infectious Diseases Society of America (IDSA): **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer**[80] **(2010)**	Initial Antibiotic Therapy
	• Oral route:
	  o For low-risk adults only; use ciprofloxacin plus amoxicillin-clavulanate
	• Monotherapy with vancomycin not indicated:
	  o Choose therapy with 1 of the following agents: cefepime or ceftazidime, or imipenem or meropenem
	• Two drugs without vancomycin:

Clinical Guideline	Recommendation(s)
	○ Choose an aminoglycoside plus antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem • Vancomycin plus 1 or 2 antibiotics: ○ Choose cefepime or ceftazidime plus vancomycin, with or without an aminoglycoside; carbapenem plus vancomycin, with or without an aminoglycoside; or antipseudomonal penicillin plus an aminoglycoside and vancomycin Modification of Therapy During the First Week of Treatment • Patient becomes afebrile in 3–5 days: ○ Adjust therapy to the most appropriate drug(s). If no etiologic agent is identified and if the patient is at low risk initially, and oral antibiotic treatment was begun with no subsequent complications, continue use of the same drugs. ○ If the patient was at low risk initially and therapy with intravenous drugs was begun with no subsequent complications, the regimen may be changed after 48 h to oral ciprofloxacin plus amoxicillin-clavulanate for adults or cefixime for children. ○ If the patient is at high risk initially with no subsequent complications, continue use of the same intravenous drugs. • Persistent fever throughout the first 3–5 days: ○ Reassess therapy on day 3. If there is no clinical worsening, continue use of the same antibiotics; stop vancomycin use if cultures do not yield organisms. ○ If there is progressive disease, change antibiotics. ○ If the patient is febrile after 5 days, consider adding an antifungal drug Antibiotic Prophylaxis for Afebrile Neutropenic Patients • Use of antibiotic prophylaxis is not routine because of emerging antibiotic resistance, except for the use of trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* pneumonitis.
American College of Rheumatology (ACR): **Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis[22] (2008)**	Monotherapy Recommendations • Initiation of methotrexate or leflunomide monotherapy for patients with all disease durations and for all degrees of disease activity, irrespective of poor prognostic features. • Hydroxychloroquine monotherapy for patients without poor prognostic features, with low disease activity, and with disease duration ≤24 months. • Minocycline monotherapy for patients without poor prognostic features, with low disease activity, and with short disease duration. • Sulfasalazine monotherapy for patients with all disease durations and without poor prognostic features and those with all degrees of disease activity. Two-drug Combination Therapy Recommendations • Methotrexate plus hydroxychloroquine for patients with moderate to high disease activity irrespective of disease duration or poor prognostic features and for patients with longer disease duration and low disease activity, independent of prognostic features. • Methotrexate plus leflunomide for patients with intermediate or longer disease duration (≥6 months), regardless of prognostic features as long as disease activity is high. • Methotrexate plus sulfasalazine for patients with all disease durations if they have high disease activity and poor prognostic features. • Hydroxychloroquine plus sulfasalazine for patients with intermediate disease duration (6–24 months) and high disease activity but without

Clinical Guideline	Recommendation(s)
	poor prognostic features. Three-drug Combination Therapy Recommendations • Sulfasalazine plus hydroxychloroquine plus methotrexate for all patients with poor prognostic features and moderate or high levels of disease activity, regardless of disease duration. Biologic Therapy Recommendations • Patients with early rheumatoid arthritis (RA) and only low or moderate disease activity are not considered candidates for biologic therapy. • The use of an anti-TNFα agent in combination with methotrexate is recommended if high disease activity was present for <3 months with features of both a poor prognosis and an absence of either barriers related to treatment cost and no insurance restrictions to accessing medical care. • In intermediate-duration and longer-duration RA, the use of an anti-TNFα agent is recommended in patients for whom prior methotrexate monotherapy led to an inadequate response, with moderate disease activity and features of a poor prognosis, and for patients with high disease activity, irrespective of prognostic features. • The use of an anti-TNFα agent is recommended in patients for whom prior methotrexate therapy was used in combination, or if sequential administration of other nonbiologic DMARDs led to an inadequate response with at least moderate residual disease activity irrespective of prognostic features. • The anti-TNFα agents (etanercept, infliximab, and adalimumab) are efficacious in improving disease activity, function, and quality of life and/or retarding radiographic progression when used alone, in combination with methotrexate, or in patients for whom treatment with DMARDs other than methotrexate led to an inadequate response.
British Society for Rheumatology (BSR): **Guideline for the Management of Rheumatoid Arthritis (The First Two Years)**[81] **(2006)**	• Patients with rheumatoid arthritis (RA) should be established on disease-modifying antirheumatic drug (DMARD) therapy as soon as possible after the diagnosis. • There is clear evidence of disease-modifying effect for methotrexate, sulfasalazine, leflunomide and intramuscular gold, with less compelling, controlled data supporting reduction of erosions with hydroxychloroquine, penicillamine, oral gold, cyclosporine and azathioprine, although these agents do improve symptoms and some objective measures of inflammation. • Choice of the first agent is based on the risk to benefit ratio with hydroxychloroquine an option in disease perceived as mild and methotrexate or sulfasalazine in those adjudged moderate-to-severe, or likely to progress.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the sulfonamides are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Sulfonamides[1-8]

Indication	Sulfadiazine	Sulfamethoxazole/ Trimethoprim	Sulfasalazine
Central Nervous System Infections			
H. influenzae meningitis (adjunctive therapy with parental streptomycin)	✔		
Meningococcal meningitis	✔		
Toxoplasmic encephalitis (adjunctive therapy with pyrimethamine)	✔		
Gastrointestinal Indications			
Prolongation of the remission period between acute attacks of ulcerative colitis			✔ †‡
Shigellosis		✔	
Traveler's diarrhea		✔	
Treatment of mild to moderate ulcerative colitis and adjunctive therapy for severe ulcerative colitis			✔ †‡
Genitourinary Infections			
Chancroid	✔		
Urinary tract infections	✔	✔	
Respiratory Infections			
Acute exacerbations of chronic bronchitis		✔	
Otitis media		✔	
Otitis media (adjunctive therapy with penicillin)	✔		
Pneumocystis carinii pneumonia		✔	
Miscellaneous Infections			
Adjunctive treatment of malaria due to chloroquine-resistant strains of *P. falciparum*	✔		
Inclusive conjunctivitis	✔		
Nocardiosis	✔		
Rheumatic fever (prophylaxis)	✔		
Toxoplasmosis			
Trachoma	✔		
Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs			✔ †
Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs			✔ †

†Delayed-release tablets
‡Immediate-release tablets

IV. Pharmacokinetics

The pharmacokinetic parameters of the sulfonamides are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Sulfonamides[1-8]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Sulfadiazine	Well absorbed	38-48	Liver	Renal (57)	7-16.8
Sulfamethoxazole and trimethoprim	90-100	S: 70 T: 44-62	Liver	S: Renal (10-30) T: Renal (50-75)	S: 6-17 T: 8-11
Sulfasalazine	<15	99	Intestinal tract	Renal (37)	4.2-11

V. Drug Interactions

Significant drug interactions with the sulfonamides are listed in Table 6.

Table 6. Significant Drug Interactions with the Sulfonamides[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Sulfamethoxazole and trimethoprim	1	Anticoagulants	Sulfamethoxazole-trimethoprim may increase the hypoprothrombinemic effects of anticoagulants, possibly with bleeding. Inhibition of the hepatic metabolism of the S(-) warfarin enantiomorph by sulfamethoxazole-trimethoprim appears to be the primary mechanism.
Sulfamethoxazole and trimethoprim	1	Dofetilide	Sulfamethoxazole-trimethoprim may increase the pharmacologic effects and plasma concentrations of dofetilide.
Sulfonamides	1	Methotrexate	The pharmacologic effects of methotrexate may be increased. Sulfonamides may displace methotrexate from plasma protein binding sites, competitively inhibit renal tubular secretion of methotrexate, and exert additive antifolate activity.
Sulfamethoxazole and trimethoprim	2	ACE Inhibitors	Hyperkalemia, possibly with cardiac arrhythmias or cardiac arrest, may occur with the combination of sulfamethoxazole-trimethoprim and ACE inhibitors. Reduction of aldosterone activity by ACE inhibitors may act, at least additively, with sulfamethoxazole-trimethoprim to decrease potassium excretion producing hyperkalemia.
Sulfamethoxazole and trimethoprim	2	Sulfones	The plasma concentrations of both drugs may be elevated.
Sulfonamides	2	Hydantoins	Pharmacologic effects of hydantoins may be increased. Inhibition of hepatic microsomal enzymes by sulfonamides may decrease the metabolic elimination of hydantoins.

Generic Name(s)	Significance Level	Interaction	Mechanism
Sulfonamides	2	Methenamine	Methenamine is contraindicated for use with sulfonamides due to the potential for formation of insoluble precipitates in the urine. Methenamine is broken down in acidic urine to formaldehyde. Insoluble precipitates may form when certain sulfonamides are exposed to formaldehyde.
Sulfonamides	2	Sulfonylureas	Certain combinations of sulfonylureas and sulfonamides may produce enhanced hypoglycemic effects. Sulfamethoxazole-trimethoprim may displace sulfonylureas from plasma protein binding sites and/or inhibit hepatic CYP2C9-mediated hepatic metabolism of sulfonylureas.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the sulfonamides are noted in Table 7. The use of sulfonamides has been associated with rare cases of fatal adverse events, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Sulfonamide therapy should be discontinued at the first sign of these serious adverse events.

Table 7. Adverse Drug Events (%) Reported with the Sulfonamides[1-8]

Adverse Events	Sulfadiazine	Sulfamethoxazole/ Trimethoprim	Sulfasalazine
Cardiovascular			
Pericarditis	-	-	✔ †‡
Pleuritis	-	-	✔ †‡
Polyarteritis nodosa	-	-	✔ †‡
Central Nervous System			
Apathy	-	✔	-
Aseptic meningitis	-	✔	-
Ataxia	✔	✔	✔ †‡
Cauda equina syndrome	-	-	✔ †‡
Chills	✔	✔	-
Depression	✔	✔	✔ †‡
Dizziness	✔	-	4‡
Drowsiness	-	-	✔ †‡
Fatigue	-	✔	-
Fever	✔	✔	≤5‡
Guillain-Barre syndrome	-	-	✔ †‡
Hallucinations	✔	✔	✔ †‡
Headache	✔	✔	≤9‡
Hearing loss	-	-	✔ †‡
Insomnia	✔	✔	✔ †‡
Kernicterus	-	✔	-
Meningitis	-	-	✔ †‡
Nervousness	-	✔	-
Peripheral neuritis	✔	✔	-

Adverse Events	Sulfadiazine	Sulfamethoxazole/ Trimethoprim	Sulfasalazine
Peripheral neuropathy	-	-	✔ †‡
Seizures	✔	✔	✔ †‡
Tinnitus	✔	✔	✔ †‡
Transverse myelitis	-	-	✔ †‡
Vertigo	✔	✔	✔ †‡
Dermatological			
Alopecia	-	-	✔ †‡
DRESS syndrome	-	-	✔ †‡
Erythema multiforme	✔	✔	-
Exfoliative dermatitis	✔	✔	✔ †‡
Henoch-Schonlein purpura	-	✔	-
Lyell's syndrome	✔	-	✔ †‡
Mucha-Habermann syndrome	-	-	✔ †‡
Photosensitivity	✔	✔	✔ †‡
Pruritus	✔	✔	≤4‡
Rash	✔	✔	≤13‡
Skin discoloration	-	-	✔ †‡
Skin eruption	✔	✔	-
Stevens-Johnson syndrome	✔	✔	✔ †‡
Toxic epidermal necrolysis	-	✔	-
Urticaria	✔	✔	✔ ‡
Endocrine and Metabolic			
Goiter production	✔	-	-
Thyroid function disturbance	✔	-	-
Gastrointestinal			
Abdominal pain	✔	✔	≤8†‡
Anorexia	✔	✔	✔ ‡
Diarrhea	✔	✔	✔ †‡
Dyspepsia	-	-	13‡
Enterocolitis	-	-	✔ †‡
Gastric distress	-	-	✔ ‡
Glossitis	-	✔	-
Nausea	✔	✔	≤19‡
Pancreatitis	✔	✔	✔ †‡
Pseudomembranous colitis	-	✔	-
Stomatitis	✔	✔	✔ †, 4‡
Vomiting	✔	✔	≤8‡
Genitourinary			
Acute nephropathy	✔	-	-
Anuria	✔	✔	✔ †‡
Crystalluria	✔	✔	✔ †‡
Diuresis	✔	✔	-
Hematuria	✔	-	✔ †‡
Hemolytic-uremic syndrome	-	-	✔ †‡
Interstitial nephritis	✔	✔	✔ †‡
Nephrotic syndrome	-	-	✔ †‡
Nephrotoxicity	-	✔	-
Oliguria	✔	✔	✔ †‡
Periarteritis nodosa	✔	✔	-
Proteinuria	-	-	✔ †‡
Renal failure	-	✔	-

Adverse Events	Sulfadiazine	Sulfamethoxazole/ Trimethoprim	Sulfasalazine
Stone formation	✔	-	-
Toxic nephrosis	✔	✔	✔ †‡
Urinary tract infections	-	-	✔ †‡
Urine discoloration	-	-	✔ †‡
Hematologic			
Agranulocytosis	✔	✔	✔ †‡
Aplastic anemia	✔	✔	✔ †‡
Cyanosis	-	-	✔ ‡
Eosinophilia	-	✔	-
Granulocytopenia	✔	-	-
Heinz body anemia	-	-	✔ ‡
Hemolysis	-	✔	-
Hemolytic anemia	✔	✔	✔ ‡
Hypoprothrombinemia	✔	✔	✔ †‡
Leukopenia	✔	✔	✔ †, 3‡
Megaloblastic anemia	-	✔	✔ †‡
Methemoglobinemia	✔	✔	✔ †‡
Myelodysplastic syndrome	-	-	✔ †‡
Neutropenia	-	✔	✔ †‡
Purpura	✔	-	✔ †‡
Thrombocytopenia	✔	✔	✔ †, 1‡
Vasculitis	-	-	✔ †‡
Hepatic			
Cirrhosis	-	-	✔ †‡
Hepatic failure	-	-	✔ †‡
Hepatic necrosis	-	-	✔ †‡
Hepatitis	✔	-	✔ †‡
Hepatotoxicity	-	✔	✔ †‡
Jaundice	✔	-	✔ †‡
Transaminases increased	-	✔	✔ †, 4‡
Laboratory Test Abnormalities			
BUN increased	-	✔	-
Hyperbilirubinemia	-	✔	-
Hyperkalemia	-	✔	-
Hypoglycemia	✔	✔	-
Hyponatremia	-	✔	-
Serum creatinine increased	-	✔	-
Musculoskeletal			
Arthralgia	✔	✔	✔ †‡
Myalgia	-	✔	-
Rhabdomyolysis	-	✔	✔ †‡
Weakness	-	✔	-
Respiratory			
Cough	-	✔	-
Dyspnea	-	✔	-
Fibrosing alveolitis	-	-	✔ †‡
Interstitial lung disease	-	-	✔ †‡
Pneumonitis	-	-	✔ †‡
Pulmonary infiltrates	-	✔	-
Other			
Allergic reaction	-	✔	-

Adverse Events	Sulfadiazine	Sulfamethoxazole/ Trimethoprim	Sulfasalazine
Allergic myocarditis	✔	✔	✔ †‡
Anaphylactoid reactions	✔	-	-
Anaphylaxis	-	✔	✔ †‡
Angioedema	-	✔	-
Conjunctival injection	✔	-	✔ †‡
Drug fever	✔	-	-
Lupus-like symptoms	-	✔	✔ †‡
Periorbital edema	✔	-	✔ †‡
Scleral injection	✔	-	✔ †‡
Serum sickness-like reactions	✔	✔	✔ †‡

✔ Percent not specified
- Event not reported
†Immediate-release formulation
‡Delayed-release formulation

VII. Dosing and Administration

The usual dosing regimens for the sulfonamides are listed in Table 8.

Table 8. Usual Dosing Regimens for the Sulfonamides[1-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Sulfadiazine	Unspecified Infections: Initially, 2 to 4 g; maintenance, 2 to 4 g, divided into 3 to 6 doses, every 24 hours	Rheumatic Fever Prophylaxis: ≥2 months of age: <30 kg: 500 mg every 24 hours ≥30 kg: 1 g every 24 hours Unspecified Infections: ≥2 months of age: Initially, one-half the 24-hour dose; maintenance, 150 mg/kg or 4 g/m^2, divided into 4 to 6 doses, every 24 hours	Tablet: 500 mg
Sulfamethoxazole and trimethoprim	Acute Exacerbations of Chronic Bronchitis: 800-160 mg every 12 hours for 14 days *Pneumocystis Carinii* Pneumonia: Prophylaxis: 800-160 mg daily Treatment: 75-100 mg/kg sulfamethoxazole and 15-20 mg/kg trimethoprim per day given in equally divided doses every 6 hours for 14 to 21 days Shigellosis: 800-160 mg every 12 hours for 5 days Traveler's Diarrhea: 800-160 mg every 12 hours for 5 days	Acute Otitis Media: ≥2 months of age: 40 mg/kg sulfamethoxazole and 8 mg/kg trimethoprim per day given in 2 divided doses every 12 hours for 10 days *Pneumocystis Carinii* Pneumonia: ≥2 months of age: Prophylaxis: 750 mg/m^2/day sulfamethoxazole and 150 mg/m^2/day trimethoprim given in equally divided doses twice daily on 3 consecutive days per week Treatment: 75-100 mg/kg sulfamethoxazole and 15-20 mg/kg trimethoprim per day given in equally divided doses every 6 hours for 14 to 21 days	Injection: 80-16 mg/ml Suspension: 200-40 mg/5 ml Tablet: 400-80 mg 800-160 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Urinary Tract Infections: 800-160 mg every 12 hours for 10-14 days	Shigellosis: ≥2 months of age: 40 mg/kg sulfamethoxazole and 8 mg/kg trimethoprim per day given in 2 divided doses every 12 hours for 5 days Urinary Tract Infections: ≥2 months of age: 40 mg/kg sulfamethoxazole and 8 mg/kg trimethoprim per day given in 2 divided doses every 12 hours for 10 days	
Sulfasalazine	Rheumatoid Arthritis: Tablet (DR): 2 g daily in 2 divided doses Ulcerative Colitis: Tablet, tablet (DR): Initial, 3 to 4 g daily in evenly divided doses; Maintenance, 2 g daily	Juvenile Rheumatoid Arthritis (Polyarticular Course): Tablet (DR): 30-50 mg/kg/day in 2 divided doses Ulcerative Colitis: ≥6 years of age: Tablet, tablet (DR): Initial, 40-60 mg/kg/day in 3-6 divided doses; Maintenance, 30 mg/kg/day divided into 4 doses	Tablet: 500 mg Tablet (DR): 500 mg

DR=delayed-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the sulfonamides are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Sulfonamides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Central Nervous System Infections				
Chirgwin et al.[25] (2002) Sulfadiazine 1,500 mg QID and atovaquone suspension 1,500 mg QD for 6 weeks of acute treatment and 42 week maintenance period vs atovaquone suspension 1,500 mg QD and pyrimethamine 200 mg on day 1, followed by 75 mg QD for 6 weeks of acute treatment and 42 week maintenance period	RCT, OL Patients with either presumptive or definitive toxoplasmic encephalitis (TE), either acute or relapsed, human immunodeficiency virus (HIV) positive or diagnosed with acquired immunodeficiency syndrome (AIDS)	N=49 48 weeks	Primary: Clinical and radiographic response to treatment for acute disease and as maintenance therapy, adverse effects	Primary: Out of patients assigned to atovaquone-pyrimethamine, 75% experienced an overall response to treatment for acute disease compared to 82% in the atovaquone-sulfadiazine group. All patients demonstrated complete resolution of lesions on radiologic examinations performed at weeks 12 and 16 during the maintenance therapy phase. Adverse events requiring treatment discontinuation occurred in 32% of patients receiving pyrimethamine and 17% of those on sulfadiazine regimen.
Torre et al.[26] (1998) Sulfadiazine (S) 60 mg/kg/day, pyrimethamine (P) 50 mg QD, folinic	RCT, PRO, MC Patients >18 years of age with AIDS and toxoplasmic encephalitis	N=77 4 months	Primary: Clinical efficacy, radiologic efficacy, death, adverse events	Primary: There was no statistically significant difference in complete clinical response rate between the P-S and the SMX-TMP groups at the end of acute therapy (65.7% vs 62.1%, respectively). A complete resolution of radiologic lesions was noted in 39.3% of patients in the P-S group compared to 62.1% patients in the SMX-TMP group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acid 10 mg QD for 4 weeks, followed by 3 months maintenance therapy at half of the original dosage vs SMX-TMP 50-10 mg/kg/day for 4 weeks, followed by 3 months maintenance therapy at half of the original dosage				(P=0.0478). There was no significant difference in survival between the two groups. Adverse effects occurred more frequently in the P-S treatment group compared to the SMX-TMP group (37.8% vs 12.5%, respectively; P=0.0162). Skin rashes were observed only in the P-S group.
Dermatological Infections				
Khawcharoenporn et al.[34] (2010) SMX-TMP 1 double strength tablet twice daily vs cephalexin 500 mg 4 times per day vs clindamycin 300 mg 4 times per day	RETRO Patients ≥18 years of age with cellulitis	N=405 Variable duration	Primary: Treatment success rate, compliance, safety	Primary: The overall treatment success rate with SMX-TMP was significantly higher than the success rate with cephalexin (91% vs 74%; P<0.001). Clindamycin success rate was higher than that of cephalexin but did not reach statistical significance (85% vs 74%; P=0.22). The success rates of SMX-TMP and clindamycin were comparable. The treatment success rate with SMX-TMP was significantly more successful than cephalexin in patients who were male (P=0.001), were Pacific Islanders (P=0.001), had diabetes mellitus (P=0.001), were obese (P=0.002), had positive cultures for MRSA (P=0.01), and were cigarette smokers (P=0.04). The treatment success rate with clindamycin was higher than with cephalexin in patients who had MRSA infections (P<0.01), had moderately severe cellulitis (P<0.03), and were obese (P<0.04). Methicillin-resistant *S. aureus* was recovered in 62% of positive culture specimens.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Compliance and adverse drug reaction rates were not significantly different among patients who received these 3 antibiotics. Factors associated with treatment failure included therapy with an antibiotic that was not active against community-associated MRSA (P<0.001) and severity of cellulitis (P<0.001).
Tong et al.[65] (2010) SMX-TMP 20 + 4 mg/kg twice daily for 5 days vs penicillin benzathine 45 mg/kg IM as a single dose	RCT Aboriginal children 2 months to 16 years of age with impetigo	N=13 7 days	Primary: Successful treatment of impetigo lesions at day 7 after the commencement of treatment Secondary: Bacterial resolution of sores at day 4 and day 7; successful treatment at day 4	Primary: Treatment was successful in all 7 patients assigned to SMX-TMP, and 5 of 6 patients assigned to the penicillin group 7 days after randomization (P=0.46). Secondary: By day 4, microbiological clearance was documented in 5 of 7 patients treated with SMX-TMP and in 2 of 6 patients treated with penicillin (P=0.28). By day 7, microbiological clearance was documented in all 7 patients treated with SMX-TMP and in 3 of 6 patients treatment with penicillin (P=0.07). Treatment was successful after 4 days in 6 of 7 treated with SMX-TMP and 3 of 6 with penicillin (P=0.27).
Gastrointestinal Infections				
Gotuzzo et al.[51] (1989) SMX-TMP 800-160 mg twice daily for 5 days vs norfloxacin 800 mg single dose	RCT Patients ≥18 years of age with clinical dysentery, >3 unformed stools with gross blood and/or mucus within 48 hours of study onset	N=55 5 days	Primary: Days to last unformed stool, total number of stools and frequency of positive stool cultures after therapy initiation	Primary: There was no statistically significant difference between the treatment groups in the duration of illness (mean, 2.5 days with SMX-TMP and 2.0 days with norfloxacin; P=0.20). There was no statistically significant difference between the treatment groups in the number of unformed stools collected after therapy initiation (mean 9.7 stools with SMX-TMP and 7.6 stools with norfloxacin; P=0.312). Only one patient in the SMX-TMP group had a positive stool sample after completion of therapy, compared to none in the ofloxacin group.
Ashkenazi et al.[52] (1993)	RCT, PRO, DB	N=77	Primary: Cure rate, stool	Primary: While only one child in the cefixime group experienced treatment failure,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SMX-TMP 50-10 mg/kg/day for 5 days vs cefixime 8 mg/kg/day for 5 days	Children aged 6 months-16 years with >2 unformed stools within 24 hours of study entry with gross blood and/or fever >38.5˚C, isolation of *Shigella* organism	5 days	cultures, clinical relapse, symptoms	31% of patients in the SMX-TMP-resistant group did not respond to therapy (P<0.001). There were no significant differences between cefixime and SMX-TMP-susceptible groups. Clinical relapse was low in both groups (<10%). After 2 days of treatment, 78% of the cefixime group had stool samples negative for *Shigella* compared to 23% of patients in the SMX-TMP-resistant group (P=0.001). All patients in the SMX-TMP-susceptible group had negative stool cultures after 2 days of treatment. The mean number of days to a negative stool culture result was 2.4 days for the cefixime group and 4.7 days for the SMX-TMP-resistant group. None of the patients in the SMX-TMP-susceptible group had a relapse, compared to 7% in the cefixime group.
Ericsson et al.[53] (1990) SMX-TMP 1,600-320 mg given as 1 dose vs SMX-TMP 800-160 mg given orally twice daily for 3 days vs loperamide hydrochloride 4 mg given as a loading dose, followed by 2 mg after each loose	RCT, DB, PC Patients with >3 unformed stools within 24 hours of study entry in addition to another symptom of enteric disease, such as abdominal cramps, nausea, or vomiting	N=227 3 days	Primary: Duration of diarrhea, failure rate	Primary: Patients treated with the combination therapy had the shortest duration of diarrhea (1 hour) compared with the placebo group (59 hours) and the 3-day SMX-TMP therapy (34 hours; P<0.005 compared with placebo). The proportion of treatment failures was significantly lower in all treatment groups compared with the placebo group (P<0.005). Patients presenting with mild diarrhea at baseline randomized to the loperamide group exhibited shorter duration of diarrhea (18 hours) compared to the placebo group (96 hours; P=0.02). Patients treated solely with loperamide exhibited longer diarrhea duration compared to patients on combination therapy (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
stool movement (maximum dose 16 mg) vs SMX-TMP 800-160 mg given orally twice daily for 3 days, in addition to loperamide hydrochloride, 4 mg given as a loading dose, followed by 2 mg after each loose stool movement (maximum dose 16 mg) vs placebo				
Green et al.[27] (2002) Sulfasalazine 333 mg 3 capsules TID vs balsalazide 750 mg 3 capsules TID	RCT, DB, MC, PG Adults >18 years of age with newly diagnosed or recently relapsed ulcerative colitis and a negative stool sample	N=57 12 weeks	Primary: Rate of remission, change in symptoms, sigmoidoscopic and histological assessments, patient assessment, adverse events	Primary: There was no significant difference in the remission rate between the sulfasalazine and balsalazine groups (59% vs 75%, respectively; P=0.19). Both groups showed a significant improvement in stool frequency over time. The proportion of patients with normal sigmoidoscopic appearances increased at each visit for both groups. Rectal biopsies taken at entry and at the final visit demonstrated similar improvements in both groups. According to patient diaries, the median number of stools with blood

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				and/or mucus decreased to zero in both treatment groups by week six and was maintained at this level through the end of the study. Fewer patients in the balsalazine group withdrew from the study due to adverse events compared to the sulfasalazine group (7% vs 31%, respectively; P=0.041).
Sood et al.[28] (2003) Sulfasalazine 6 g daily vs azathioprine 2.5 mg/kg/day	RCT, OL, PRO Adults >18 years of age with newly diagnosed or recently relapsed ulcerative colitis	N=25 18 months	Primary: Treatment failure (either disease relapse or drug withdrawal because of adverse effects)	Primary: Five of 12 patients in the azathioprine group and 8 of 13 patients in the sulfasalazine group had sustained remission during the study period of 18 months. The difference between the two groups was not statistically significant. Two patients in the azathioprine group had to stop therapy due to adverse effects (bone marrow suppression and acute pancreatitis). All patients in the azathioprine group who had treatment failure developed it in the first half of the study while patients in the sulfasalazine group experienced treatment failure throughout the study.
Sutherland et al.[29] (2006) Sulfasalazine vs 5-aminosalicylic acid	MA Patients with active mild-moderate ulcerative colitis	12 studies At least 4 weeks	Primary: Failure to induce either a complete global or clinical remission, endoscopic improvement, adverse effects	Primary: There was no statistically significant difference in the failure to induce either a complete global or clinical remission between 5-aminosalicylic acid and sulfasalazine (OR=0.83; 95% CI, 0.42 to 1.13). There was no statistically significant difference in the failure to induce endoscopic improvement between 5-aminosalicylic acid and sulfasalazine (OR=0.66; 95% CI, 0.42 to 1.04). There were significantly more withdrawals due to side effects with sulfasalazine compared to 5-aminosalicylic acid.
Sutherland et al.[30] (2006) Sulfasalazine vs 5-aminosalicylic	MA Patients with active mild-moderate ulcerative colitis	N=1,598 (11 studies) At least 7 months	Primary: Failure to maintain either a complete global or clinical remission, adverse effects	Primary: Sulfasalazine was found to be more efficacious in terms of maintaining either a complete global or clinical remission compared to 5-aminosalicylic acid (OR=1.29; 95% CI, 1.05 to 1.57). There was no statistically significant difference in the number of withdrawals due to side effects between the two groups (OR=1.31; 95% CI, 0.86 to 1.99).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acid				
Nikfar et al.[66] (2009) Sulfasalazine (SSZ) vs mesalamine	MA Patients with mild-to-moderate ulcerative colitis	19 trials Variable duration	Primary: Overall improvement, relapse rate, total adverse events, and withdrawals because of adverse events	Primary: The summary relative risk (RR) for overall improvement in four trials that compared SSZ and mesalamine was 1.04 (95% CI, 0.89–1.21; P=0.63). The summary RR for relapse in six trials that compared SSZ and mesalamine was 0.98 (95% CI, 0.78–1.23; P=0.85). Data on adverse events in studies that compared SSZ and mesalamine yielded an overall RR of 0.76 (95% CI, 0.54–1.07; P=0.11). The summary RR for withdrawals because of adverse events in eight trials that compared SSZ and mesalamine was 0.78 (95% CI 0.46–1.3; P=0.33).
Loftus et al.[31] (2004) Mesalazine, olsalazine, or balsalazide vs placebo or sulfasalazine	MA Patients with active ulcerative colitis	N=6,031 (46 studies) 2-12 weeks	Primary: Adverse events, withdrawal due to adverse events	Primary: One study of mesalazine vs sulfasalazine for active colitis showed significantly fewer patients with adverse events with mesalazine. Both balsalazide vs sulfasalazine studies for active disease showed significantly fewer withdrawals with balsalazide. One trial of balsalazide vs sulfasalazine for maintenance showed significantly fewer patients with adverse events with balsalazide. Otherwise, no significant differences in safety outcomes were noted.
Genitourinary Infections				
Tran et al.[58] (2001) SMX-TMP 40-80 mg/kg/day for 1-3 days (short-treatment course) vs SMX-TMP 40-80 mg/kg/day for 7-14	MA Children <18 years of age with uncomplicated cystitis confirmed by urine culture	N=1,279 (22 trials) Up to 14 days	Primary: Cure rate, adverse events	Primary: There was no difference between short- and long-courses of SMX-TMP in terms of cure rates (difference in cure rate, 6.24%; 95% CI, -3.74 to 16.2%). The short-course amoxicillin therapy was less effective in curing the infection compared to the conventional length of therapy (difference in cure rate, 13%; 95% CI, 4 to 24). Consequently, 8 patients would need to receive a conventional amoxicillin course of therapy to prevent 1 treatment failure that would have occurred with a shorter duration of treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days (long-treatment course) or amoxicillin for 1-3 days (short-treatment course) vs amoxicillin for 7-14 days (long-treatment course)				Drug-related toxicity increased in proportion to the length of therapy.
Mårild et al.[64] (2009) SMX-TMP 3-15 mg/kg oral suspension twice daily for 10 days vs ceftibuten 9 mg/kg oral suspension once daily for 10 days	RCT, OL, MC Patients 1 month to 12 years of age with a first-time febrile urinary tract infection (UTI)	N=547 14 to 20 days	Primary: Bacteriological and clinical outcomes	Primary: In the intention-to-treat population, the bacteriological elimination rates in the ceftibuten and SMX-TMP groups were 91% and 95%, respectively (P=NS). In the per protocol population, the bacteriological elimination rates in the ceftibuten and SMX-TMP groups were 91% and 97%, respectively (P<0.01). In the intention-to-treat population, the clinical cure rates among patients treated with ceftibuten and SMX-TMP were 93% and 83%, respectively (P=0.008). In the per protocol population, the clinical cure rates were 93% and 90%, respectively (P=NS). Adverse events were reported by 3% of the patients in the ceftibuten group and by 5% in the SMX-TMP group (P=NS). Gastrointestinal symptoms were reported most frequently. There were no serious adverse events reported.
McCarty et al.[55] (1999)	RCT, MC Women ≥18 years	N=688 Up to 6 weeks	Primary: Pathogen eradication rate,	Primary: End-of-study evaluation revealed a lack of statistically significant difference in the pre-treatment pathogen eradication rate between the study

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SMX-TMP 800-160 mg twice daily for 3 days vs ciprofloxacin 100 mg twice daily for 3 days vs ofloxacin 200 mg twice daily for 3 days	of age with primary UTI, confirmed by a positive urine culture obtained within 48 hours of study onset, presenting with signs and symptoms of dysuria, pyuria, and urinary frequency for <10 days duration		clinical response rate (resolution of symptoms), relapse rate, premature discontinuation, adverse events	groups. Pathogen eradication occurred in 94% of ciprofloxacin, 93% of SMX-TMP, and 97% of ofloxacin-treated patients. At the 4-6 week follow-up evaluation, recurrence rates were 11% in the ciprofloxacin, 16% in the SMX-TMP, and 13% in the ofloxacin-treated group. Clinical success at the end of therapy was 31% in the ciprofloxacin, 41% in the SMX-TMP, and 39% in the ofloxacin-treated group. The frequency of adverse effects was 93% in the ciprofloxacin, 95% in the SMX-TMP, and 96% in the ofloxacin-treated group (P=0.03). Premature discontinuation of the study drug due to side effects was more common in the SMX-TMP group, compared to the ciprofloxacin and ofloxacin groups (P=0.02).
Iravani et al.[56] (1999) SMX-TMP 800-160 mg tablets twice daily for 7 days vs ciprofloxacin 100 mg tablets twice daily for 3 days, followed by placebo for the remaining 4 days vs nitrofurantoin 100 mg capsules twice	RCT, DB, MC Women ≥18 years of age with primary UTI, confirmed by a positive urine culture obtained within 48 hours of study onset, signs and symptoms of dysuria, pyuria, and urinary frequency for <10 days duration	N=713 Up to 6 weeks	Primary: Pathogen eradication after 4-10 days of therapy, clinical response rate (resolution of symptoms), relapse rate, adverse events	Primary: Bacterial eradication was similar in the three treatment groups (ciprofloxacin 88%; SMX-TMP 93%; and nitrofurantoin 86%). At the 4-6 week follow-up, ciprofloxacin had statistically higher eradication rates (91%) compared to SMX-TMP (79%; 95% CI, -20.6 to -3.9) and nitrofurantoin (82%; 95% CI, -17.1 to -0.9). Clinical resolution 4-10 days after therapy initiation and at the 4-6 week follow-up was similar among the three treatment groups. The frequency of adverse effects was not statistically different among the three treatment groups (P=0.093). However, ciprofloxacin caused fewer incidences of nausea compared to either of the other medications (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for 7 days				
Gupta et al.[36] (2007) SMX-TMP 800-160 mg tablets twice daily for 3 days vs nitrofurantoin 100 mg twice daily for 5 days	RCT, OL Women18 to 45 years of age who had symptoms of acute cystitis (dysuria, frequency, and/or urgency) and a urine culture with at least 102 CFU/mL of a uropathogen	N=338 35 days	Primary: Clinical cure rate at the end of the entire study period (30 days after therapy) Secondary: Clinical and microbiological cure rates at the early follow-up visit (5-9 days after therapy)	Primary: Clinical cure was achieved in 79% of the trimethoprim-sulfamethoxazole group and in 84% of the nitrofurantoin group (95% confidence interval, -13% to 4%; P=0.25). Secondary: Clinical and microbiological cure rates at the first follow-up visit were similar in the trimethoprim-sulfamethoxazole group and the nitrofurantoin group. Among women treated with trimethoprim-sulfamethoxazole, there was a statistically significant decrease in clinical cure in women who had a trimethoprim sulfamethoxazole–non-susceptible uropathogen compared with women who had a susceptible isolate. Overall, 84% of trimethoprim-sulfamethoxazole–treated women with a trimethoprim-sulfamethoxazole–susceptible uropathogen had a clinical cure compared with 41% with a trimethoprim-sulfamethoxazole–non-susceptible uropathogen (P<0.001). Microbiological cure was achieved in 97% of trimethoprim-sulfamethoxazole–treated women with a trimethoprim-sulfamethoxazole–susceptible isolate vs 65% of women with a trimethoprim-sulfamethoxazole–non-susceptible isolate (P<0.001).
Buckwold et al.[54] (1982) SMX-TMP 800-160 mg 2 tablets as a single dose vs SMX-TMP 1,600-320 mg 4 tablets as a single dose vs	RCT, MC Women with symptoms suggestive of acute cystitis (dysuria, frequency of urination, suprapubic discomfort)	N=117 Up to 4 weeks	Primary: Pathogen eradication rate, clinical response rate (resolution of symptoms), relapse rate, premature discontinuation, adverse events	Primary: Overall cure rates varied from 85%-95%, but there was no statistically significant difference between the study groups (P>0.05). SMX-TMP regimens were associated with a significantly greater minimum inhibitory concentration (MIC) at 24 hours postdose compared to the sulfisoxazole group (P<0.001). None of the regimens predisposed patients to re-infection (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sulfisoxazole 1 g 2 tablets as a single dose vs sulfisoxazole 2 g 2 tablets as a single dose				
Varde et al.[57] (1981) SMX-TMP 80/400 mg 2 tablets BID for 14 days vs trimethoprim-sulfadiazine (TMP-SD) 75/225 mg 2 tablets BID for 14 days	RCT Patients 11 to 66 years of age with an uncomplicated urinary tract infection confirmed by urine culture	N=37 14 days	Primary: Microbiological and clinical response, adverse events	Primary: The number of patients exhibiting good response (defined as symptomatic improvement with sterile urine culture after 3 days of treatment) was greater in the TMP-SD group compared to the SMX-TMP group (74% vs 61%, respectively). While 37% of patients in the TMP-SD group exhibited clinical response (defined as being asymptomatic on the first day of treatment with significant bacteriuria), 44% of patients in the SMX-TMP group exhibited a clinical response. Only one patient in the TMP-SD group developed a macular rash, which was the only adverse event observed during the study period.
Respiratory Infections				
Chintu et al.[50] (2004) SMX-TMP 240 mg suspension daily (children <5 years of age); 480 mg suspension daily (children ≥5 years of age) vs	RCT, DB Children 1-14 years of age with a positive HIV antibody test and, for those younger than 18 months of age, clinical features suggestive of an HIV infection	N = 534 19 months	Primary: Mortality, hospitalization, adverse events, PCP	Primary: The study was conducted in an area of high SMX-TMP resistance (60-80%). A 33% reduction in mortality was seen in the SMX-TMP group compared to placebo (RR, 0.67; 95% CI, 0.53 to 0.85). SMX-TMP was associated with a statistically significant reduction in hospitalization rate compared to placebo (RR, 0.77; 95% CI, 0.62 to 0.96). There was no significant difference in adverse effects between the two groups (P=0.06).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				This benefit applied across all ages (test for heterogeneity P=0.82) and baseline CD4 counts (test for heterogeneity P=0.36). *P carinii* was identified in only one (placebo) of 73 nasopharyngeal aspirates from children with pneumonia.
Sachs et al.[40] (1995) SMX-TMP 800-160 mg BID for 7 days in addition to oral corticosteroids vs amoxicillin 500 mg TID for 7 days in addition to oral corticosteroids vs oral corticosteroids	RCT, DB Patients ≥18 years of age with asthma or chronic obstructive pulmonary disease (COPD)	N=195 14 days	Primary: Peak expiratory flow (PEF)	Primary: PEF percent predicted assessed during an exacerbation improved significantly in all three groups over the 14-day observation period (P<0.001), ranging from 0.34%-0.78% predicted per day, finally returning to baseline value. No statistically significant difference was observed between the groups. There was no statistically significant difference between the groups in symptom scores, expressed as slopes or absolute values from days 1-14. The decrease in the symptom severity scores was significant in all three groups (P<0.001). There was no statistically significant difference between the three groups in terms of treatment failure rate.
Knowles et al.[44] (1980) SMX-TMP 800-160 mg BID for 10 days vs amoxicillin 500 mg TID for 10 days vs	RCT Patients ≥18 years of age hospitalized for an acute exacerbation of chronic bronchitis, defined as an increase in cough, breathlessness, and volume of sputum, with sputum color changes	N=29 10 days	Primary: Mucoid sputum at the time of discharge, conversion of sputum from purulent to mucoid, sputum volume reduction, length of admission, clinical improvement (50% reduction in illness	Primary: The number of patients failing to achieve mucoid sputum at the time of discharge was not significantly different between the SMX-TMP (45%), amoxicillin (88%), and erythromycin groups (46%). There were no significant differences between the groups in terms of time to conversion of sputum from purulent to mucoid, sputum volume reduction, length of admission, clinical improvement, and change in lung function. Significantly more patients on the erythromycin therapy experienced at least one side effect compared to the amoxicillin group (P<0.025).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
erythromycin stearate 500 mg TID for 10 days			severity), and change in lung function, adverse events	
Feldman et al.[59] (1990) SMX-TMP 40-8 mg/ml suspension BID for 10 days vs amoxicillin-clavulanate 50 mg/kg/day divided into 2 doses for 10 days	RCT, DB Patients 1 to 14 years of age with signs/symptoms of acute otitis media and an acoustic reflectometer reading of at least 5 units	N=219 10 days	Primary: Cure or improvement rate, failure rate, compliance rate, side effects	Primary: Compared to amoxicillin-clavulanate, SMX-TMP led to significantly higher cure or improvement rate (82% vs 93%, respectively; P=0.03). Compared to amoxicillin-clavulanate, SMX-TMP was associated with a significantly lower treatment failure rate (18% vs 7%, respectively; P=0.03). Compliance rates were not significantly different between the amoxicillin-clavulanate and SMX-TMP groups (84% and 76%, respectively). Amoxicillin-clavulanate was associated with a significantly greater incidence of gastrointestinal side effects, principally diarrhea, compared to SMX-TMP (P<0.0001). Rash developed in 4 children treated with SMX-TMP.
Takata et al.[62] (2001) SMX-TMP vs amoxicillin-clavulanate vs cefaclor vs ceftriaxone	MA Children1 to 18 years of age with uncomplicated acute otitis media	5 trials Up to 21 days	Primary: Clinical failure, adverse effects	Primary: Children with acute otitis media not treated with antibiotics experienced a 1-7-day clinical failure rate of 19%. Amoxicillin treatment reduced the 2-7-day clinical failure rate by 12% (95% CI, 0.04 to 0.20). The pooled clinical failure rate difference at 14 days for the 3 studies comparing cefaclor with SMX-TMP showed no significant difference. The remaining studies compared various antibiotics with ampicillin or amoxicillin or amoxicillin-clavulanate with SMX-TMP. No difference in clinical failure rates was noted in these studies.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Chodosh et al.[43] (1982) SMX-TMP 800-160 mg BID for 14 days vs ampicillin 500 mg, 1 capsule QID for 14 days	RCT, DB, XO Patients ≥18 years of age with chronic bronchitis who developed an acute bronchial infectious exacerbation within 2 weeks of the study *Pseudomonas, Klebsiella*, or *S aureus* were isolated	N=21 14 days	Primary: Chest symptoms, physical findings, vital signs, pulmonary function, laboratory values, sputum analysis, time to recurrence of exacerbation	Primary: Patients in the ampicillin group experienced a longer recurrence-free time compared to patients in the SMX-TMP group (P<0.05). Sputum volumes decreased significantly in each treatment group, starting on day 3 of the study (P<0.05). While none of the patients in the ampicillin group discontinued therapy due to adverse effects, 3 patients in the SMX-TMP group discontinued treatment. There were no significant differences noted between the two study drugs in all other outcome measures.
Feder et al.[61] (1982) SMX-TMP 37.5-7.5 mg/kg/day divided into two doses for 14 days vs ampicillin 70 mg/kg/day divided into 4 doses for 14 days vs amoxicillin 30 mg/kg/day divided into 3 doses for 14 days	RCT, DB Patients 2 months to 7 years of age with signs/symptoms of otitis media in addition to a bulging tympanic membrane with decreased mobility	N=282 14 days	Primary: Premature discontinuation of therapy due to ≥5 watery stools per day, diarrhea	Primary: Therapy was discontinued in significantly more ampicillin-treated patients compared with amoxicillin-treated patients (P<0.01) or SMX-TMP-treated patients (P<0.03). Among patients who completed a full course of therapy, significantly more ampicillin-treated patients developed diarrhea compared with amoxicillin-treated patients (P<0.04) or SMX-TMP-treated patients (P<0.02). Initial symptom resolution occurred after approximately 2 days of treatment in all three groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Marchant et al.[60] (1984) SMX-TMP 40-8 mg/kg/day divided into 2 doses for 10 days vs cefaclor 40 mg/kg/day divided into 2 doses for 10 days	RCT, DB Children 2 to 24 months of age with otitis media based on the presence of otoscopic signs of middle ear effusion and a recent history of fever or irritability, confirmed by tympanocentesis	N=129 4 weeks	Primary: Bacteriologic cure rate, clinical cure rate, failure rate, side effects	Primary: SMX-TMP was associated with a greater bacterial eradication rate (95%) compared to cefaclor (70%; P=0.017). There were no significant differences in clinical outcomes between patients taking SMX-TMP and those on cefaclor therapy. Diarrhea was more common in the cefaclor group (22%) compared with the SMX-TMP group (10%; P=0.08).
Anderson et al.[45] (1981) SMX-TMP 800-160 mg BID for 7 days vs cefaclor 500 mg TID for 10 days	RCT, DB Patients ≥18 years of age admitted to the hospital with acute exacerbation of chronic bronchitis	N=39 7 days	Primary: Sputum analysis, PEF rate, adverse effects	Primary: While all pathogens were eradicated in the SMX-TMP group, bacteria were isolated in 4 patients (20%) on cefaclor therapy. Sputum remained purulent in 16% of patients on SMX-TMP therapy and 35% of patients receiving cefaclor. There were no statistically significant differences between the groups in the PEF rate during the study period. There were no drug-induced side effects in either of the two groups.
Nouira et al.[35] (2010) SMX-TMP 800/160 mg twice daily for 10 days vs ciprofloxacin 750 mg twice daily for 10 days	RCT, DB Patients ≥40 years of age with an acute exacerbation of COPD requiring mechanical ventilation	N=170 10 days	Primary: Hospital death and need for an additional course of antibiotics Secondary: Duration of mechanical ventilation, length of hospital stay, and exacerbation-	Primary: Combined hospital death and additional antibiotic prescription rates were similar in the 2 groups (16.4% vs 15.3% in the SMX-TMP vs ciprofloxacin group; 95% CI, -9.8% to 12.0%; P=0.832). During the study, 15 patients died in the hospital, 7 (8.2%) in the SMX-TMP group and 8 (9.4%) in the ciprofloxacin group (P>0.05). Secondary: The mean EFI was similar in both treatment groups (83 days vs 79 days in the SMX-TMP vs ciprofloxacin group; P=0.41).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			free interval (EFI)	Of 38 patients initially receiving noninvasive ventilation in the SMX-TMP group, 17 (45%) were secondarily intubated versus 13 (34%) in the ciprofloxacin group (P=0.347). The duration of mechanical ventilation and length of hospital stay were similar in the 2 study groups. Adverse events were minor and comparably distributed in both treatment groups.
Toma et al.[46] (1998) SMX-TMP 1,600-320 mg (≥60 kg) or 1,200-240 mg (<60 mg) QID for 21 days vs clindamycin 450 mg QID and primaquine 15 mg QD for 21 days	RCT, DB, MC Patients ≥16 years of age with human immunodeficiency virus (HIV)-related PCP	N=116 21 days	Primary: Treatment success (>2-point improvement in the PCP score, calculated on the basis of body temperature, respiratory rate, cough, chest tightness, dyspnea, supplemental oxygen requirements, and chest radiograph), steroid use, duration of therapy, adverse events	Primary: There was no statistically significant difference in the duration of therapy between the treatment groups (P=0.68). The treatment success rates for SMX-TMP and clindamycin-primaquine were 76% and 74%, respectively. There were no statistically significant differences between the treatment regimens with respect to dyspnea scores, PCP scores and lactate dehydrogenase values at any time. There was no statistically significant difference between treatment groups with respect to the use of steroids (12 patients per group; P=0.74). There was no significant difference in the rate of PCP recurrence between the two treatment arms (P=0.99). There was no significant difference in the rate of adverse effects experienced by the two treatment groups (P=0.57). Rash was the most frequent side effect in both groups. The incidence of rash was similar in both groups (P=0.78).
Perez-Gonzalvo et al.[41] (1996) SMX-TMP 800-160 mg BID for 10 to 14 days vs	RCT, OL, PG Patients with acute exacerbation of chronic bronchitis, presenting with increased cough and/or dyspnea, sputum volume, or	N=162 30 days	Primary: Clinical response, clinical failure, bacteriologic response	Primary: Clinical response was observed in significantly more patients on ofloxacin therapy (80.2%) compared with patients in the SMX-TMP group (51.9%; P<0.0002; 95% CI, 14.5% to 42.3%). Bacterial eradication occurred in 50% of patients in the ofloxacin group compared with 29.1% of patients in the SMX-TMP group (P=0.032; 95% CI, 3% to 38.9%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ofloxacin 400 mg QD for 10 to 14 days, which could be increased to 400 mg BID if improvement was not seen after 72 hours of therapy	sputum purulence, chronic cough and sputum production for >2 consecutive years and on most days for 3 consecutive months			Re-infection occurred in 33.3% of patients on ofloxacin therapy compared with 7.3% of patients in the SMX-TMP group. Six patients in the SMX-TMP group and 7 patients in the ofloxacin group experienced an adverse effect attributable to antibiotic therapy.
Boye et al.[42] (1991) SMX-TMP 2 tablets for 10 days vs ofloxacin 200 mg BID for 10 days	RCT, DB Patients ≥18 years of age with exacerbations of COPD or chronic bronchitis with increased cough, sputum volume, and purulence	N=137 10 days	Primary: Clinical improvement or cure, clinical failure rate, bacteriological efficacy, adverse effects	Primary: Clinical improvement or cure occurred in 80.9% of the ofloxacin-treated patients and in 72.4% of patients on SMX-TMP therapy (P=0.266). The failure rate was significantly lower in the ofloxacin group compared with the SMX-TMP group (3.2% vs 13.8%, respectively). Relapse was seen in 15.9% of patients on ofloxacin therapy compared with 13.8% of patients in the SMX-TMP group (P=0.047). Severe adverse reactions were reported by three patients in the ofloxacin group compared with 8 patients in the SMX-TMP group. While 13 organisms were identified in patients on ofloxacin therapy, only 6 organisms were isolated from the SMX-TMP-treated patients.
Klein et al.[47] (1992) SMX-TMP 100-20 mg/kg/day IV divided into 4 doses vs pentamidine 4 mg/kg/day IV administered over 1 hour	RCT, DB, PRO Patients with PCP, confirmed by either a bronchoalveolar lavage or lung biopsy	N=163 21 days	Primary: Treatment failure (defined as persistent fever, worsening hypoxemia, and/or progressive roentgenographic deterioration), change in therapy due to toxicity, 5-day mortality rate, survival rate,	Primary: Slightly more patients in the SMX-TMP group (42%) experienced treatment failure compared to the pentamidine group (40%; P=0.733). Slightly more patients in the SMX-TMP group (34%) had to discontinue therapy due to toxicity compared to the pentamidine group (25%; P=0.235). The mortality rate during the first five days of therapy was 4% in each of the two treatment groups (P=0.984). The overall survival rates were similar in the SMX-TMP (67%) and pentamidine groups (74%; P=0.402).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			adverse effects	The survival rates for patients requiring a change in therapy because of failure to respond was 46% for the SMX-TMP group compared with 56% for the pentamidine group. When a change in therapy was made because of toxicity, survival rates were 97% for those receiving SMX-TMP versus 94% for those receiving pentamidine.
Ioannidis et al.[48] (1996) SMX-TMP vs pentamidine vs dapsone-based regimen vs placebo	MA Patients ≥18 years of age with HIV	N=6,583 (35 trials) Up to 2 years	Primary: PCP events, PCP-related mortality, all-cause mortality, toxoplasmosis events	Primary: SMX-TMP was effective in preventing PCP infection; the failure rate was close to zero (0.5%). Patients randomized to SMX-TMP exhibited less prophylactic failures (42% reduction; 95% CI, 24% to 55%) compared to patients receiving aerosolized pentamidine. The overall rate of treatment-limiting adverse events (per 100 patient-years) was 19 (95% CI, 18 to 21) for SMX-TMP and 15 (95% CI, 14 to 17) for dapsone-based regimens. The risk of adverse effects requiring SMX-TMP discontinuation decreased by 43% in patients taking SMX-TMP three times weekly as opposed to once daily (95% CI, 30% to 54%).
Green et al.[37] (2007) SMX-TMP vs pentamidine vs atovaquone	MA Immuno-compromised patients with cancer, bone marrow transplant patients, solid organ transplant patients, patients receiving corticosteroids, patients receiving	N=1,155 (11 trials) Variable duration	Primary: *Pneumocystis* infections Secondary: All-cause mortality, PCP-related mortality, infections other than *Pneumocystis*	Primary: There was a significant reduction in the occurrence of PCP infections in the SMX-TMP prophylaxis group compared to others, RR 0.09 (95% CI 0.02 to 0.32). The corresponding number of patients needed to treat (NNT) to prevent one episode of PCP was 15 patients (95% CI, 13 to 20). Five trials compared daily-administrated TMP/ SMX prophylaxis versus no intervention or placebo. Prophylaxis resulted in a significant decrease in the occurrence of PCP infections, RR 0.08 (95% CI, 0.02 to 0.38). Three trials compared SMX-TMP prophylaxis versus a non anti-PCP antibiotic (quinolones). Prophylaxis with SMX-TMP was better than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs dapsone vs pyrimethamine vs clindamycin vs mycophenolate mofetil	other immune suppressive medications, severe malnutrition, primary immune-deficiency diseases			quinolones in the prevention of PCP, RR 0.09 (95% CI, 0.01 to 1.57). Secondary: All-cause mortality was reported in five trials. Three trials compared SMX-TMP to placebo, RR 0.79 (95% CI 0.18 to 3.46), and two trials compared SMX-TMP versus quinolones, RR 0.49 (95% CI, 0.02 to 10.73). SMX-TMP prophylaxis reduced PCP-related mortality, RR 0.17 (95% CI, 0.03 to 0.94). Four trials compared SMX-TMP versus no intervention or placebo. PCP related mortality was reduced in the prophylaxis group, RR 0.18 (95% CI, 0.02 to 1.56). Three studies compared SMX-TMP versus quinolones. PCP related mortality was reduced in the SMX-TMP group, RR 0.14 (95% CI, 0.01 to 2.65). In the analysis of any infection other than PCP, 0ne study comparing SMX-TMP prophylaxis versus no intervention or placebo found no statistically significant difference between the groups, RR 0.86 (95% CI, 0.68 to 1.08). Three studies that compared SMX-TMP prophylaxis versus quinolones found significantly more infections other than PCP in the SMX-TMP arm compared to quinolones, RR 1.59 (95% CI, 1.17 to 2.14).
Bucher et al.[49] (1997) SMX-TMP 800-160 mg daily to 3 times weekly vs pentamidine 300-400 mg monthly to 300 mg bimonthly vs dapsone 50 mg QD	MA Patients with HIV receiving antiretroviral (ARV) treatment	N=4,832 (22 trials) Mean 13.2 months	Primary: PCP events, all-cause mortality, toxoplasmosis events, drug-related toxicity	Primary: The risk ratio of dapsone-pyrimethamine compared to pentamidine in terms of PCP infection was 0.90 (95% CI, 0.71 to 1.15), 0.72 for toxoplasma encephalitis (95% CI, 0.54 to 0.97), and 1.07 (95% CI, 0.90 to 1.27) for mortality. Patients with higher CD4 counts at baseline (>100 cells/mm3) were found to be at a higher risk for experiencing drug-related toxicity compared to those with lower CD4 cell counts (P=0.01). High-dose dapsone-pyrimethamine regimens (≥200/50 mg) were more effective compared to the low-dose regimens. Compared to aerosolized pentamidine, SMX-TMP was more effective at reducing the rate of PCP infections (RR, 0.59; 95% CI, 0.45 to 0.76). However the difference in the risk of toxoplasma encephalitis (RR, 0.78;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 100 mg twice weekly or dapsone-pyrimethamine 350-50 mg weekly				95% CI, 0.55 to 1.11) and mortality (RR, 0.88; 95% CI, 0.74 to 1.06) was not statistically significant. SMX-TMP was more effective at preventing PCP infections in patients with higher CD4 counts at baseline (>100 cells/mm^3) compared to those with lower CD4 cell counts (P=0.02). Compared to dapsone-pyrimethamine, SMX-TMP was more effective at reducing the rate of PCP infections (RR, 0.49; 95% CI, 0.26 to 0.92). However the difference in the risk of toxoplasma encephalitis (RR, 1.17; 95% CI, 0.26 to 2.18), mortality (RR, 0.98; 95% CI, 0.80 to 1.08), and drug-limiting toxicity (RR, 1.08; 95% CI, 0.88 to 1.25) was not statistically significant. The reduction of mortality risk due to SMX-TMP treatment was greater among patients with lower CD4 counts at baseline (<100 cells/mm3) compared to those with higher CD4 cell counts (P=0.03). Drug limiting toxicity was experienced by 31.5%, 29.7%, and 6.8% of patients treated with SMX-TMP, dapsone-pyrimethamine, and aerosolized pentamidine, respectively. Compared with aerosolized pentamidine, SMX-TMP administered to 100 patients will prevent 3-7 cases of PCP at a risk of 21 additional patients experiencing toxicity.
Miscellaneous				
Soheilian et al.[23] (2005) <u>Regimen A:</u> Sulfadiazine 2 g for 2 days, followed by sulfadiazine 500 mg every 6 hours, pyrimethamine 100 mg QD for 2 days, followed by 25 mg	RCT, SB, AC, PRO Patients with ocular toxoplasmosis	N=59 24 months	Primary: Changes in retinochoroidal lesion size at 6 weeks, difference in visual acuity (VA), adverse events, rate of recurrence	Primary: Active toxoplasmosis retinochoroiditis resolved in all patients over the treatment phase of the study. There was no significant difference in mean reduction of retinochoroidal lesion size between the patients randomized to receive regimens A and B (61% vs 59% reduction, respectively; P=0.75). No significant difference in VA between the regimen A and B groups (P=0.56). Adverse effects were similar in both groups with only one patient in each

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD, and folinic acid 5 mg QD for 6 weeks; prednisone 1 mg/kg QD was started from the third day of therapy and tapered off over 2 weeks vs Regimen B: SMX-TMP 400 mg-80 mg 2 tablets every 12 hours for 6 weeks; prednisone 1 mg/kg QD was started from the third day of therapy and tapered off over 2 weeks				group experiencing rash as the only significant drug-related side effect. There was no significant difference in the rate of recurrence between the regimen A and B groups after 24 months of follow-up (10.3% vs 10%, respectively; P=0.64).
Bosch-Driessen et al.[24] (2002) Regimen A: Sulfadiazine 4 g QD, pyrimethamine 100 mg on day 1, followed by 50 mg QD, and folinic acid 15 mg QD for 4 weeks; prednisone 40 mg QD was started from the third day	RCT, OL, MC, AC Patients, 16 to 80 years of age with an active toxoplasmic retinochoroidal lesion located centrally within the major temporal vascular arcades or a juxtapapillary lesion	N=46 24 months	Primary: Time of intraocular inflammation resolution, size of the retinochoroidal lesion, difference in visual acuity (VA), side effects	Primary: There was no significant difference in the duration of intraocular inflammation between the regimen A and B groups (P=0.96). There was no significant difference in the decrease in size of the retinochoroidal lesion between the regimen A and B groups 3 months after study onset (P=0.32). There was no significant difference in the decrease in VA between the regimen A and B groups (P=0.72). There was no significant difference in the rate of recurrence between the regimen A and B groups during the 24 months of follow-up (56% vs 33%, respectively; P=0.10).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
of therapy and tapered off after 10 days vs Regimen B: Pyrimethamine 100 mg on day 1, followed by 50 mg QD, azithromycin 250 mg QD or 500 mg QOD, and folinic acid 15 mg QD for 4 weeks; prednisone 40 mg QD was started from the third day of therapy and tapered off after 10 days				Adverse effects were more frequent in the sulfadiazine group compared to the azithromycin group (64% vs 33%; P<0.04). Thrombocytopenia as well as an elevation in serum creatinine and liver enzymes was observed in both groups.
Suarez-Almazor et al.[32] (2000) Sulfasalazine vs placebo	MA Patients with rheumatoid arthritis (RA)	N=468 (6 trials) ≥6 months	Primary: Failure to maintain either a complete global or clinical remission, adverse effects	Primary: In the pooled analysis, sulfasalazine was more efficacious compared to placebo in the number of tender joints (standardized weighed mean difference= -0.49; 95% CI, -0.75 to -0.36). In the pooled analysis, sulfasalazine was more efficacious compared to placebo in the number of swollen joints (standardized weighed mean difference= -0.49; 95% CI, -0.79 to -0.12). In the pooled analysis, sulfasalazine was more efficacious compared to placebo in pain severity (standardized weighed mean difference= -0.42; 95% CI, -0.72 to -0.12). In the pooled analysis, sulfasalazine was more efficacious compared to placebo in erythrocyte sedimentation rate (ESR) (standardized weighed mean difference= -17.6 mm; 95% CI, -0.64 to 0.00).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Withdrawals from adverse effects were significantly higher in the sulfasalazine group (OR=3.0). Patients receiving placebo were 4 more times more likely to discontinue treatment because of lack of efficacy than patients receiving sulfasalazine.
van Rossum et al.[38] (2007) Sulfasalazine 50 mg/kg/day vs placebo	PRO, SB Patients 2 to 18 years, with onset of juvenile idiopathic arthritis (JIA) before the age of 16, at least 1 joint with active arthritis, and an insufficient response to nonsteroidal anti-inflammatory (NSAID) drug therapy	N=61 7-10 years	Primary: Disease outcomes over time	Primary: Active joints were present in 74% of the patients, including 30% with active polyarthritis. Compared with the end of the trial, follow-up of both groups combined showed a significant increase in joint limitation, but a stable situation in clinical parameters and acute phase reactants. The median C-HAQ for the whole group was 0.25 (range 0 to 2). None to mild disability was reported by 74% of the patients, moderate disability by 20% and severe disability by 6% of the patients. At follow up, 53% of patients in the sulfasalazine group were on DMARDs, including 4 still on sulfasalazine. The median duration of sulfasalazine treatment was 2.5 years. Over the follow-up period, 50% of sulfasalazine patients were switched to another DMARD treatment, including methotrexate in 47%. The median duration of methotrexate treatment was 3 years. The median number of DMARDs used in the follow-up period was 1.5 (range 1 to 5). At follow-up, 72% of patients in the placebo group were on DMARDs, including 4 patients on sulfasalazine. The median duration of sulfasalazine treatment in the placebo group was significantly longer than in the sulfasalazine group (5.2 years). Over the follow-up period, 64% of the placebo group switched to other DMARDs, including methotrexate (55% of the patients). The median duration of methotrexate treatment was 4 years. The median number of DMARDs used in the follow-up period by the placebo group was 2 (range 0 to 5).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				At follow-up, 47% of the sulfasalazine patients were classified as ACR Pedi 30 responders compared with the placebo patients (P=0.02).
Capell et al.[39] (2007) Phase I Sulfasalazine enteric-coated tablets 500 mg daily, increasing by 500 mg weekly until the target dose of 40 mg/kg/day (or the maximum tolerated dose) Phase II Sulfasalazine at the dose achieved by 6 months with the addition of methotrexate initially 7.5 mg/week, increasing by 2.5 mg/month until the maximal permitted dose of 25 mg or toxicity occurred vs sulfasalazine at the dose achieved by 6 months, with the addition of placebo	OL (Phase I), RCT (Phase II) Patients 18 to 80 years of age and with rheumatoid arthritis, disease duration <10 years, and active disease defined by the disease activity score (DAS) of >2.4. Patients with DAS ≥ 2.4 after 6 months were included in phase II.	Phase I N=687 6 months Phase II N=165 18 months	Primary: Reduction in DAS at 18 months Secondary: Proportion of patients achieving a good response as determined by the European League Against Rheumatism (EULAR) criteria (DAS <2.4, and a fall in score from baseline by 1.2) and American college of Rheumatology (ACR) 20, 50 and 70 responses, safety	Primary: At 18 months, DAS was significantly lower in those who received combination treatment compared with those who received either sulfasalazine or methotrexate alone, but the two monotherapy arms were not significantly different (combination vs sulfasalazine P=0.039; combination vs methotrexate P=0.023; sulfasalazine vs methotrexate P=0.79). Secondary: For change in EULAR DAS in the three groups, there was a trend for more patients to be in the remission or good DAS category in the combination group and fewer in the high DAS group at 18 months. ACR 20, 50 and 70 responses indicate that the combination group achieved a higher proportion in the 20%, 50% and 70% responding groups compared with the single drugs alone, although this was not statistically significant. Radiographic examination showed no significant difference in total Sharp score and in total erosions (hands and feet), and joint space narrowing between 6 and 18 months in the SASP, MTX and combination groups was similar, with no significant difference between the three groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo with the addition of methotrexate initially 7.5 mg/week, increasing by 2.5 mg/month until the maximal permitted dose of 25 mg or toxicity occurred				
Braun et al.[68] (2011) Sulfasalazine titrated to a maximum of 3 g/day for 16 weeks vs etanercept 50 mg once weekly for 16 weeks	RCT, DB, MC Patients with active ankylosing spondylitis (AS)	N=566 16 weeks	Primary: Proportion of patients who achieved the Assessment of SpondyloArthritis international Society criteria for 20% improvement (ASAS20) at 16 weeks Secondary: Proportion of responders according to the ASAS20 response criteria at prespecified visits up to week 16, as well as the proportion of patients meeting	Primary: A total of 75.9% patients receiving etanercept achieved an ASAS20 response at week 16, compared with 52.9% of the patients in the sulfasalazine group (P<0.0001). Secondary: A significantly greater proportion of patients in the etanercept group than in the sulfasalazine group achieved an ASAS20 response as early as week 2 of treatment (P<0.0001); this difference was sustained through week 16. The proportions of patients receiving etanercept who achieved ASAS40 and ASAS5/6 responses were significantly higher at all time points, as early as week 2 and through week 16, when compared with the proportions of patients receiving sulfasalazine who achieved these end points (P<0.0001). An ASAS40 response was achieved by 59.8% of etanercept-treated patients compared with 32.6% of sulfasalazine-treated patients at week 16 (P<0.0001). The percentage of patients achieving an ASAS5/6 response after 16 weeks was significantly greater in the etanercept group (45.5%) compared with the sulfasalazine group (21.2%; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			the ASAS 40% improvement criteria (ASAS40) and the proportion achieving ASAS 20% improvement in 5 of 6 domains (ASAS5/6) at prespecified visits up to week 16	The percentage of patients achieving partial remission was significantly higher in the group receiving etanercept compared with the group receiving sulfasalazine, as early as week 2 through week 16 (P<0.001). At week 16, 33.3% of patients in the etanercept group and 15.5% of patients in the sulfasalazine group achieved partial remission (P<0.0001). Improvements in mobility (on the BASMI), disease activity (on the BASDAI), and physical function (on the BASFI) were significantly greater in the etanercept group than in the sulfasalazine group at all time points (P<0.0001). The improvement in the mean BASMI from baseline to week 16 was 25.6% in the etanercept group compared with 7.9% in the sulfasalazine group (P<0.0001). The mean BASDAI improved 54.1% in etanercept-treated patients compared with 33.3% in sulfasalazine-treated patients from baseline to week 16 (P<0.0001). The mean BASFI improved by 47.8% in the etanercept group compared with 28.5% in the sulfasalazine group (P<0.0001). Treatment-emergent adverse events (AEs) were reported in 55.3% of patients in the study. The proportions of patients who reported a treatment-emergent AE or AE of special interest were similar in the etanercept group and the sulfasalazine group. A significantly greater number of patients in the etanercept group than in the sulfasalazine group reported experiencing injection-site reactions (10.8% vs 1.6%, respectively; P<0.001. Other common AEs reported in the etanercept and sulfasalazine groups were upper respiratory tract infection (8.2% and 9.1%, respectively), headache (7.7% and 11.2%, respectively), and nausea (6.6% and 9.6%, respectively).
Combe et al.[33] (2009) Sulfasalazine 2 to 3 g daily vs etanercept 25 mg	RCT, DB, MC Patients ≥ 18 years of age with active adult onset rheumatoid arthritis and disease duration of ≤20 years	N=260 2 years	Primary: Disease activity, disease remission, percentage of patients achieving 20% or greater improvement (ACR 20), ACR response rates	Primary: Disease activity (as assessed by mean DAS) was significantly lower in the groups receiving etanercept than in the group receiving sulfasalazine from week 2 to week 104 (P<0.01). Significantly lower mean DAS values were observed during weeks 68–104 for the combination group compared with the etanercept alone group (P<0.05). A significantly higher proportion of patients receiving the combination or etanercept had a low level of disease activity compared with those receiving sulfasalazine after 6 months, which was maintained throughout the 2 years (P<0.01); at 2 years, 57.0% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SQ twice weekly vs sulfasalazine 2 to 3 g daily plus etanercept 25 mg SQ twice weekly			(ACR 20, ACR 50 and ACR 70), disease activity score (DAS) and morning stiffness in minutes	patients receiving combination, 45.6% receiving etanercept and 4.0% receiving sulfasalazine. The proportion of patients achieving disease remission was significantly higher with the etanercept groups compared with the sulfasalazine group (P<0.01). Treatment response as assessed by ACR 20 was achieved by a significantly higher percentage of patients receiving etanercept, added to or in place of sulfasalazine, compared with those receiving sulfasalazine (P<0.01). These significant differences in treatment response among the groups were also seen using ACR 50 (P<0.01) and ACR 70 (P<0.01) criteria. Response rates were not significantly different between the two groups receiving etanercept. Mean HAQ values for the etanercept and combination groups were significantly lower than those for the sulfasalazine group from week 2 (P<0.01, sulfasalazine vs etanercept or combination) and these differences were sustained for the remainder of the 2-year study10 (P<0.01).
Song et al.[69] (2011) Sulfasalazine 2 to 3 g per day vs etanercept 25 mg SC twice weekly Sulfasalazine patients could be switched to methotrexate (15–20 mg weekly).	RCT, OL, MC Patients 18 to 50 years of age with non-steroidal anti-inflammatory drug-refractory axial spondyloarthritis with a symptom duration of <5 years	N=76 48 weeks	Primary: Change of active inflammatory lesions in the sacroiliac joints and spine on MRI Secondary: Reduction of active inflammatory lesions on the posterior elements of the spine and a reduction of peripheral enthesitis on MRI	Primary: At week 48, the reduction of the sacroiliac joint score from 7.7 at baseline to 2.0 with etanercept was significantly larger than the sulfasalazine group (decrease from 5.4 at baseline to 3.5; P=0.02). Secondary: At week 48, the reduction of inflammation in the spine from 2.2 at baseline to 1.0 in the etanercept group was significantly larger than the sulfasalazine group (decrease from 1.4 at baseline to 1.3; P=0.01). The number of enthesitic sites improved significantly from 26 to 11 in the etanercept group versus 24 to 26 in the sulfasalazine group (P=0.04). At week 48, 50% of patients reached clinical remission in the etanercept group versus 19% in the sulfasalazine group.
van Vollenhoven et al.[67]	RCT, MC	N=258	Primary: Achievement of a	Primary: At 12 months, 25% of patients receiving sulfasalazine and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Sulfasalazine 1,000 mg twice daily or hydroxy-chloroquine 400 mg daily plus methotrexate vs infliximab 3 mg/kg IV at weeks 0, 2, 6 and every 8 weeks thereafter plus methotrexate	Patients ≥18 years of age with early rheumatoid arthritis (symptom duration <1 year) who had received methotrexate for 3 to 4 months and had not achieved low disease activity	12 months	good response according to European League Against Rheumatism (EULAR) criteria at 12 months Secondary: Achievement of a good or moderate response with EULAR criteria, and ACR 20, ACR 50, and ACR 70	hydroxychloroquine and 39% of patients receiving infliximab had a good response according to EULAR criteria (P=0.0160). Secondary: At 12 months, 49% of patients receiving sulfasalazine and hydroxychloroquine and 60% of patients receiving infliximab had a good or moderate response according to EULAR criteria (P=0.0817). At 12 months, 28% of patients receiving sulfasalazine and hydroxychloroquine and 42% of patients receiving infliximab achieved ACR 20 (P=0.0266). At 12 months, 15% of patients receiving sulfasalazine and hydroxychloroquine and 25% of patients receiving infliximab achieved ACR 50 (P=0.0424). At 12 months, 7% of patients receiving sulfasalazine and hydroxychloroquine and 12% of patients receiving infliximab achieved ACR 70 (P=0.2044). Adverse events were similar among the treatment groups and accorded with known adverse events of the drugs used. No deaths occurred in either group.

Drug regimen abbreviations: BID=twice daily, PO=by mouth, QD=once daily, QID=four times daily, QOD=every other day, TID=three times daily
Study design abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OL=open label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized trial, RR=risk ratio, SB=single-blind, SMX-TMP=sulfamethoxazole/trimethoprim, XO=crossover

Additional Evidence

Dose Simplification
In a meta-analysis of 22 studies, Tran et al. reported no difference in cure rates between short courses (1-3 days) and long courses (7-14 days) of sulfamethoxazole/trimethoprim for the treatment of uncomplicated cystitis in children <18 years of age.[58]

Stable Therapy
In a randomized, double-blind, crossover trial, El-Chaar et al. evaluated the differences in taste and adherence with brand and generic antibiotic suspensions in children.[63] While there was no difference in adherence, children verbally expressed a preference for Bactrim® compared to the generic sulfamethoxazole/trimethoprim product (P=0.0342).

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Sulfonamides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Sulfadiazine	tablet	N/A	N/A	$$$$$
Sulfamethoxazole and trimethoprim	injection, suspension, tablet	Bactrim®*, Bactrim DS®*, Septra DS®*	$$$	$-$$$
Sulfasalazine	delayed-release tablet, tablet	Azulfidine®*	$$$	$

*Generic is available in at least one dosage form or strength.
N/A=not available

X. Conclusions

The sulfonamides are effective for the treatment of a variety of conditions, and the FDA-approved indications vary depending on the agent. Sulfadiazine and sulfamethoxazole/trimethoprim are approved to treat a variety of infections, including central nervous system, dermatological, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-6] Sulfasalazine is approved for the treatment of ulcerative colitis and rheumatoid arthritis. [1-3,7-8] All of the sulfonamides are available in a generic formulation.

There are many guidelines that define the appropriate place in therapy for the sulfonamides. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the sulfonamide. Sulfadiazine and sulfamethoxazole/trimethoprim are recommended as specific therapy for the treatment of susceptible pathogens causing encephalitis, diabetic foot infections, urinary tract infections, infectious exacerbations of COPD, prophylaxis/treatment of *Pneumocystis (carinii) jiroveci* pneumonia (PCP), prophylaxis/treatment of *Toxoplasma* encephalitis, as well as for the secondary prevention of rheumatic fever.[13-15,19,71,74,82] They are recommended as an alternative treatment option for meningitis, skin and soft-tissue infections, granuloma inguinale, otitis media, sinusitis, and pertussis.[9,12,18,72,76,78] Sulfasalazine is recommended as one of several initial treatment options for ulcerative colitis and rheumatoid arthritis.[10,22,81] There are very few clinical studies that directly compare the efficacy and safety of the sulfonamides.[23,26,54,57] However, the sulfonamides been shown to be comparable in efficacy to antibacterial agents in other classes.[23,25-28,34-36,39-40,42-44,46-47,51,55-56,60,62,64-65]

The use of sulfonamides has been associated with rare cases of fatal adverse events, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Sulfonamide therapy should be discontinued at the first sign of these serious adverse events.

There is insufficient evidence to support that one brand sulfonamide is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand sulfonamides within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand sulfonamide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2011. Available from Wolters Kluwer Health, Inc. Accessed November 2011.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2011; November 2011.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November 2011.
4. Bactrim® [package insert]. Philadelphia, PA: AR Scientific, Inc.; June 2010.
5. Bactrim DS® [package insert]. Philadelphia, PA: AR Scientific, Inc.; June 2010.
6. Septra DS® [package insert]. Bristol, TN: King Pharmaceuticals, Inc.; September 2006.
7. Azulfidine® [package insert]. New York, NY: Pfizer, Inc.; October 2009.
8. Azulfidine EN-tabs® [package insert]. New York, NY: Pfizer, Inc.; October 2009.
9. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004; 39(9):1267-84.
10. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010;105:501-23.
11. Hill DR, Ericsson CD, Pearson RD, Keystone JS, Freedman DO, Kozarsky PE, et al. The practice of travel medicine: Guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006; 43:1499-1539.
12. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1-110.
13. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 91: Treatment of urinary tract infections in nonpregnant women. Obstet Gynecol 2008;111:785-94.
14. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20.
15. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2010. 117 p. Available at: www.goldcopd.com. Accessed October 2011.
16. Braman SS. Chronic cough due to chronic bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129 (1 Suppl): 104S-15S.
17. Braman SS. Chronic cough due to acute bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129 (1 Suppl): 95S-103S.
18. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatrics. 2004 May;113(5):1451-65.
19. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009;58(RR-4):1-207.
20. Chaudhuri A, Martinez-Martin P, Kennedy PG, Andrew Seaton R, Portegies P, Bojar M, Steiner I; EFNS Task Force. EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. Eur J Neurol 2008;15:649-59.
21. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2006; 48(3):e1-148.
22. Saag K, Teng G, Patkar N, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762-784.
23. Soheilian M, Sadoughi MM, Ghajarnia M, et al. Prospective randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine and sulfadiazine in the treatment of ocular toxoplasmosis. Ophthalmology 2005; 112:1876-82.

24. Bosch-Driessen L, Verbraak FD, Suttorp-Schulten MSA, et al. A prospective, randomized trial of pyrimethamine and azithromycin vs pyrimethamine and sulfadiazine for the treatment of ocular toxoplasmosis. Am J Ophthalmol. 2002; 134:34-40.
25. Chirgwin K, Hafner R, Leport C, et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome: ACTG 237/ANRS 039 Study. Clin Infect Dis. 2002; 34:1243-50.
26. Torre D, Casari S, Speranza P, et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Antimicrob Agents Chemother. 1998; 42(6):1346-9.
27. Green J, Mansfield JC, Gibson JA, et al. A double-blind comparison of balsalazide, 6.75 g daily, and sulfasalazine, 3 g daily, in patients with newly diagnosed or relapsed active ulcerative colitis. Aliment Pharmacol Ther. 2002; 16:61-8.
28. Sood A, Midha V, Sood N, et al. Azathioprine versus sulfasalazine in maintenance of remission in severe ulcerative colitis. Indian J Gastroenterol. 2003; 22(3):79-81.
29. Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006 Apr 19; (2):CD000543.
30. Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006 Apr 19; (2):CD000544.
31. Loftus EV, Kane SV, Bjorkman D. Systemic review: short-term adverse effects of 5-aminosalicylic acid agents in the treatment of ulcerative colitis. Aliment Pharmacol Ther. 2004; 19:179-89.
32. Suarez-Almazor ME, Belseck E, Shea B, et al. Sulfasalazine for rheumatoid arthritis. Cochrane Database Syst Rev. 2000; (2):CD000958.
33. Combe B, Codreanu C, Fiocco U, et al. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. Ann Rheum Dis 2009;68:1146-52.
34. Khawcharoenporn T, Tice A. Empiric outpatient therapy with trimethoprim-sulfamethoxazole, cephalexin, or clindamycin for cellulitis. Am J Med 2010;123:942-50.
35. Nouira S, Marghli S, Besbes L, et al. Standard versus newer antibacterial agents in the treatment of severe acute exacerbation of chronic obstructive pulmonary disease: a randomized trial of trimethoprim-sulfamethoxazole versus ciprofloxacin. Clin Infect Dis 2010;51:143-9.
36. Gupta K, Hooton T, Roberts P. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Arch Intern Med 2007;167:2207-12.
37. Green H, Paul M, Vidal L, et al. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD005590.
38. van Rossum M, van Soesbergen R, Boers M, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis 2007;66:1518-24.
39. Capell H, Madhok R, Porter D, et al. Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from the double-blind placebo-controlled MASCOT study. Ann Rheum Dis 2007;66:235-41.
40. Sachs A, Koeter G, Groenier H, et al. Changes in symptoms, peak expiratory flow, and sputum flora during treatment with antibiotics of exacerbations in patients with chronic obstructive pulmonary disease in general practice. Thorax 1995; 50(7):758-63.
41. Perez-Gonzalvo ME, Mosquera-Pestana JO, Ramos D, et al. Ofloxacin versus trimethoprim-sulfamethoxazole in the treatment of patients with acute exacerbation of chronic bronchitis. Clin Ther. 1996; 18(3):440-6.
42. Boye NP, Gaustad P. Double-blind comparative study of ofloxacin (Hoe 280) and trimethoprim-sulfamethoxazole in the treatment of patients with acute exacerbations of chronic bronchitis and chronic obstructive lung disease. Infection 1991; 19 (7 suppl): 388-90.
43. Chodosh S, Eichel B, Ellis C, et al. Comparison of trimethoprim-sulfamethoxazole with ampicillin in acute infectious exacerbations of chronic bronchitis: a double-blind crossover study. Rev Infect Dis. 1982: 4(2): 517-25.
44. Knowles GK, Chir B, Milton AF, et al. A preliminary comparison of erythromycin, co-trimoxazole and amoxicillin in patients with acute exacerbations of chronic bronchitis admitted to hospital. J Int Med Res. 1980; 8 (2 suppl): 51-8.

45. Anderson G, Williams L, Pardoe T, et al. Co-trimoxazole versus cefaclor in acute on chronic bronchitis. J Antimicrob Chemother. 1981; 8: 487-9.
46. Toma E, Thorne A, Singer J, et al. Clindamycin with primaquine vs trimethoprim-sulfamethoxazole therapy for mild and moderately severe *Pneumocystis carinii* pneumonia in patients with AIDS: a multicenter, double-blind, randomized trial (CTN 004). Clin Infect Dis. 1998; 27:524-30.
47. Klein NC, Duncanson FP, Lenox TH. Trimethoprim-sulfamethoxazole versus pentamidine for *Pneumocystis carinii* pneumonia in AIDS patients: results of a large prospective randomized treatment trial. AIDS 1992; 6(3):301-5.
48. Ioannidis J, Cappelleri J, Skolnik P, et al. A meta-analysis of the relative efficacy and toxicity of *Pneumocystis carinii* prophylactic regimens. Arch Int Med. 1996; 156(2):177-88.
49. Bucher H, Griffith L, Guyatt G, et al. Meta-analysis of prophylactic treatments against *Pneumocystis carinii* pneumonia and toxoplasma encephalitis in HIV-infected patients. JAIDS 1997; 15(2):104-14.
50. Chintu C, Bhat G, Walker A, et al. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. Lancet 2004; 364(9448):1865-71.
51. Gotuzzo E, Oberhelman RA, Maguina C, et al. Comparison of single-dose treatment with norfloxacin and standard 5-day treatment with trimethoprim-sulfamethoxazole for acute shigellosis in adults. Antimicrob Agents Chemother. 1989; 33(7):1101-4.
52. Ashkenazi S, Amir J, Waisman Y, et al. A randomized, double-blind study comparing cefixime and trimethoprim-sulfamethoxazole in the treatment of childhood shigellosis. J Pediatr. 1993; 123(5):817-21.
53. Ericsson CD, DuPont HL, Mathewson JJ, et al. Treatment of traveler's diarrhea with sulfamethoxazole and trimethoprim and loperamide. JAMA 1990; 263(2):257-61.
54. Buckwold FJ, Ludwig P, Harding GK, et al. Therapy for acute cystitis in adult women: randomized comparison of single-dose sulfisoxazole vs trimethoprim-sulfamethoxazole. JAMA 1982; 247(13):1839-42.
55. McCarty JM, Richard G, Huck W, et al. A randomized trial of short-course ciprofloxacin, ofloxacin, or trimethoprim/sulfamethoxazole for the treatment of acute urinary tract infection in women. Am J Med. 1999; 106:292-9.
56. Iravani A, Klimberg I, Briefer C, et al. A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy with co-trimaxozole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. JAC 1999; 43:67-75.
57. Varde AB, Shetty HG, Jadav SK, et al. Comparison of trimethoprim in combination with sulfadiazine or sulfamethoxazole in the treatment of urinary tract infections. JPGM 1981; 27(3):154-8.
58. Tran D, Muchant DG, Aronoff SC. Short-course versus conventional length antimicrobial therapy for uncomplicated lower tract urinary tract infections in children: a meta-analysis of 1279 patients. J Pediatr. 2001; 139:93-9.
59. Feldman W, Sutcliffe T, Dulberg C. Twice daily antibiotics in the treatment of acute otitis media: trimethoprim-sulfamethoxazole versus amoxicillin-clavulanate. Can Med Assoc J. 1990; 142(2):115-8.
60. Marchant CD, Shurin PA, Turcysk VA, et al. A randomized controlled trial of cefaclor compared with trimethoprim-sulfamethoxazole for treatment of acute otitis media. J Pediatr. 1984; 105(4):633-8.
61. Feder HM. Comparative tolerability of ampicillin, amoxicillin, and trimethoprim-sulfamethoxazole suspensions in children with otitis media. Antimicrob Agents Chemother. 1982; 21(3):426-7.
62. Takata GS, Chan LS, Shekelle P, et al. Evidence of management of acute otitis media: role of antibiotics in treatment of uncomplicated acute otitis media. Pediatrics 2001; 108(2):239-47.
63. El-Chaar G, Gisele M, Wehlou K, et al. Randomized, double-blind comparison of brand and generic antibiotic suspensions: a study of taste and compliance in children. Pediatr Infect Dis J. 1996; 15(1):18-22.
64. Mårild S, Jodal U, Sandberg T, et al. Ceftibuten versus trimethoprim-sulfamethoxazole for oral treatment of febrile urinary tract infection in children. Pediatr Nephrol 2009;24:521-6.
65. Tong SY, Andrews RM, Kearns T, et al. Trimethopim-sulfamethoxazole compared with benzathine penicillin for treatment of impetigo in Aboriginal children: a pilot randomised controlled trial. J Paediatr Child Health 2010;46:131-3.
66. Nikfar S, Rahimi R, Rezaie A, Abdollahi M. A meta-analysis of the efficacy of sulfasalazine in comparison with 5-aminosalicylates in the induction of improvement and maintenance of remission in patients with ulcerative colitis. Dig Dis Sci 2009;54:1157-70.
67. van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet 2009;374:459-66.

68. Braun J, van der Horst-Bruinsma IE, Huang F, et al. Clinical efficacy and safety of etanercept versus sulfasalazine in patients with ankylosing spondylitis: a randomized, double-blind trial. Arthritis Rheum 2011;63:1543-51.
69. Song IH, Hermann K, Haibel H, et al. Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. Ann Rheum Dis 2011;70:590-6.
70. World Gastroenterology Organization (WGO). WGO practice guideline: acute diarrhea. Munich, Germany: World Gastroenterology Organization (WGO); 2008 Mar. 28 p. http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/01_acute_diarrhea.pdf. Accessed December 2011.
71. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM, Whitley RJ, Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303-27.
72. Chaudhuri A, Martinez-Martin P, Kennedy PG, Andrew Seaton R, Portegies P, Bojar M, Steiner I; EFNS Task Force. EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. Eur J Neurol 2008;15:649-59.
73. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005 Nov 15;41(10):1373-406.
74. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, LeFrock JL, Lew DP, Mader JT, Norden C, Tan JS; Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004 Oct 1;39(7):885-910.
75. Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, et al; Infectious Diseases Society of America. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis. 2001;32:331-51.
76. Slavin R, Spector S, Bernstein IL, et al; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol. 2005;116(6):S13-S47.
77. American Academy of Pediatrics subcommittee on the management of sinusitis and committee on quality improvement. Clinical practice guideline: management of sinusitis. Pediatrics. 2001;108(3):798-808.
78. Tiwari T, Murphy TV, Moran J; National Immunization Program, CDC. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines. MMWR Recomm Rep 2005;54(RR-14):1-16.
79. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52:1-38.
80. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR, Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:e56-93
81. Luqmani R, Hennell S, Estrach C, et al. British Society for Rheumatology; British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group. British Society for Rheumatology and british health professionals in Rheumatology guideline for the management of rheumatoid arthritis (the first two years). Rheumatology (Oxford). 2006 Sep;45(9):1167-9.
82. Bonow R, Carabello B, Chatterjee K et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e1-142.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Tetracyclines
AHFS Class 081224
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I. Overview

The tetracyclines are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-8] They bind reversibly to the 30S subunit of bacterial ribosomes and exert a bacteriostatic effect by blocking protein synthesis.[9-11]

The tetracyclines exhibit broad-spectrum antibacterial activity and are most active against aerobic gram-positive and gram-negative bacteria. They also have activity against many atypical pathogens. The widespread use of the tetracyclines has led to an increase in resistance. Cross-resistance has also been reported among the various agents. Tigecycline has been shown to have activity against tetracycline-resistant pathogens.[9-11] It is not affected by the two major tetracycline-resistance mechanisms, ribosomal protection and efflux. There has been no cross-resistance observed between tigecycline and other antibacterials.[8]

The tetracyclines that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Demeclocycline, doxycycline, minocycline and tetracycline are available in a generic formulation. This class was last reviewed in August 2009.

Table 1. Tetracyclines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Demeclocycline	tablet	N/A	demeclocycline
Doxycycline	capsule, delayed-release tablet, injection, suspension, syrup, tablet	Adoxa®*, Adoxa Pak®*, Doryx®*, Morgidox®*, Vibramycin®*	doxycycline
Minocycline	capsule, tablet	Dynacin®*	minocycline
Oxytetracycline	injection	Terramycin®, Terramycin IM®	none
Tetracycline	capsule	N/A	tetracycline
Tigecycline	injection	Tygacil®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

The tetracyclines have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the tetracyclines that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Tetracyclines[1-8]

Organism	Demeclocycline	Doxycycline	Minocycline	Oxytetracycline	Tetracycline	Tigecycline
Gram-Positive Organisms						
Bacillus anthracis	✔	✔	✔	✔	✔	
Enterococcus faecalis		✔			✔	✔
Enterococcus faecium		✔			✔	
Listeria monocytogenes	✔	✔	✔	✔	✔	
Staphylococcus aureus	✔		✔	✔		✔
Staphylococcus epidermidis						✔
Streptococci, viridans group					✔	
Streptococcus agalactiae						✔
Streptococcus anginosus						✔
Streptococcus pneumoniae	✔	✔	✔	✔	✔	✔
Streptococcus pyogenes		✔		✔	✔	✔
Gram-Negative Organisms						
Acinetobacter species	✔	✔	✔	✔	✔	
Bacteroides species		✔		✔	✔	✔
Bartonella bacilliformis	✔	✔	✔	✔	✔	
Brucella species	✔	✔	✔	✔	✔	
Calymmatobacterium granulomatis	✔	✔	✔		✔	
Campylobacter fetus	✔		✔	✔	✔	
Citrobacter freundii						✔
Enterobacter aerogenes	✔	✔	✔	✔	✔	
Enterobacter cloacae						✔
Escherichia coli	✔	✔	✔	✔	✔	✔
Francisella tularensis	✔	✔	✔	✔	✔	
Haemophilus ducreyi	✔	✔	✔	✔	✔	
Haemophilus influenzae	✔	✔	✔	✔	✔	✔
Klebsiella species	✔	✔	✔	✔	✔	✔
Legionella pneumophila						✔
Neisseria gonorrhoeae	✔	✔	✔	✔	✔	
Neisseria meningitidis			✔			
Shigella species	✔	✔	✔	✔	✔	
Vibrio cholerae	✔	✔	✔	✔	✔	
Yersinia pestis	✔	✔	✔	✔	✔	
Miscellaneous Organisms						
Actinomyces species	✔	✔	✔	✔	✔	
Balantidium coli		✔			✔	

Organism	Demeclocycline	Doxycycline	Minocycline	Oxytetracycline	Tetracycline	Tigecycline
Borrelia recurrentis	✔	✔	✔	✔	✔	
Chlamydophila psittaci	✔	✔	✔	✔	✔	
Chlamydia trachomatis	✔	✔	✔	✔	✔	
Clostridium species	✔	✔	✔	✔	✔	✔
Entamoeba species	✔	✔	✔		✔	
Fusobacterium nucleatum	✔	✔	✔	✔	✔	
Mycobacterium marinum			✔			
Mycoplasma pneumoniae	✔	✔	✔	✔	✔	
Peptostreptococcus micros						✔
Plasmodium falciparum		✔				
Propionibacterium acnes	✔	✔	✔		✔	
Rickettsia species	✔	✔	✔	✔	✔	
Treponema pallidum	✔	✔	✔	✔	✔	
Treponema pertenue	✔	✔	✔	✔	✔	
Ureaplasma urealyticum	✔	✔	✔		✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the tetracyclines are summarized in Table 3.

Table 3. Treatment Guidelines Using the Tetracyclines

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Guidelines on the Prevention, Diagnosis, and Treatment of Infective Endocarditis[78] (2009)**	• Antibiotic treatment of infective endocarditis due to oral streptococci and group D streptococci: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin or ceftriaxone for 4 weeks ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for 2 weeks ▪ Vancomycin for 4 weeks (in beta-lactam allergic patients) o Penicillin-resistant strains: ▪ Penicillin G or amoxicillin for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks plus gentamicin for 2 weeks (in beta-lactam allergic patients) • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for 4 to 6 weeks plus gentamicin for 3 to 5 days ▪ Vancomycin for 4 to 6 weeks plus gentamicin for 3 to 5 days (penicillin-allergic patients or methicillin-resistant staphylococci) o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks ▪ Vancomycin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks (penicillin-allergic patients or methicillin-resistant staphylococci) • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains ▪ Amoxicillin plus gentamicin for 4 to 6 weeks ▪ Ampicillin plus gentamicin for 4 to 6 weeks ▪ Vancomycin plus gentamicin for 6 weeks • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months ▪ Doxycycline plus quinolone for >18 months o *Bartonella* species: ▪ Ceftriaxone or ampicillin IV ▪ Doxycycline orally for 6 weeks plus gentamicin or netilmicin for 3 weeks o *Legionella* species: ▪ Erythromycin IV for 2 weeks, then orally for 4 weeks plus rifampin or ciprofloxacin orally for 6 weeks

Clinical Guideline	Recommendation(s)
	o *Mycoplasma* species: ▪ Newer fluoroquinolones for >6 months o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Penicillin G or streptomycin IV for 2 weeks, then cotrimoxazole orally for 1 year ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis (before or without pathogen identification): o Native valves: ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks o Prosthetic valves (early, <12 months post surgery) ▪ Vancomycin IV for 6 weeks, gentamicin IV for 2 weeks, and rifampin orally for 2 weeks o Prosthetic valves (late, ≥12 months post surgery) ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks
American College of Cardiology (ACC)/American Heart Association (AHA): **2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease[79] (2008)**	<u>Endocarditis Prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with CHD o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30-60 minutes before procedure): o Oral: amoxicillin o Unable to take oral medications: Ampicillin, cefazolin or ceftriaxone o Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis* o Penicillin G or ceftriaxone for 4 weeks o Ceftriaxone plus gentamicin for 2 weeks o Vancomycin for 4 weeks in patients allergic to penicillin • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin o Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2

Clinical Guideline	Recommendation(s)
	weeks o Vancomycin for 4 weeks in patients allergic to penicillin • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin o Ampicillin for 4 to 6 weeks or penicillin G plus gentamicin for 4 to 6 weeks o Vancomycin plus gentamicin for 6 weeks in patients allergic to penicillin • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials o Oxacillin-susceptible strains ▪ Nafcillin or oxacillin for 6 weeks plus the optional addition of gentamicin for 3 to 5 days ▪ Cefazolin for 6 weeks with the optional addition of gentamicin in patients allergic to penicillin o Oxacillin-resistant strains ▪ Vancomycin for 6 weeks o Oxacillin-resistant strains • Therapy for prosthetic valve endocarditis caused by staphylococci o Oxacillin-susceptible strains ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks o Oxacillin-resistant strains ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks • Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms o Ceftriaxone for 4 weeks o Ampicillin-sulbactam for 4 weeks o Ciprofloxacin for 4 weeks • Therapy for culture-negative endocarditis including *Bartonella* endocarditis o Native valve ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for 4 to 6 weeks o Prosthetic valve (early; ≤1 year) ▪ Vancomycin for 6 weeks, plus gentamicin for 2 weeks, plus cefepime for 6 weeks, plus rifampin for 6 weeks o Prosthetic valve (late; >1 year) ▪ Suspected *Bartonella*, culture negative • Ceftriaxone for 6 weeks plus gentamicin with/without doxycycline for 6 weeks ▪ Documented *Bartonella*, culture positive • Doxycycline for 6 weeks plus gentamicin for 2 weeks
American Heart Association (AHA): **Infective Endocarditis: Diagnosis, Antimicrobial Therapy, and Management of Complications**[80] **(2005)**	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus bovis*: o Penicillin-susceptible strains ▪ Penicillin G or ceftriaxone for 4 weeks ▪ Penicillin G or ceftriaxone plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Penicillin-resistant strains:

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	▪ Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus bovis*: o Penicillin-susceptible strains ▪ Penicillin G or ceftriaxone for 6 weeks with or without gentamicin for 2 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Penicillin-resistant strains: ▪ Penicillin G or ceftriaxone for 6 weeks plus gentamicin for 6 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for 6 weeks with the option of adding gentamicin for 3-5 days ▪ For penicillin-allergic individuals: cefazolin for 6 weeks with the option of adding gentamicin for 3-5 days o Oxacillin-resistant strains ▪ Vancomycin for 6 weeks • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) o Oxacillin-resistant strains ▪ Vancomycin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) • Therapy for native valve or prosthetic valve enterococcal endocarditis o Strains susceptible to penicillin, gentamicin, and vancomycin: ▪ Ampicillin or penicillin G plus gentamicin for 4-6 weeks ▪ Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Strains susceptible to penicillin, streptomycin, and vancomycin and resistant to gentamicin: ▪ Ampicillin or penicillin G plus streptomycin for 4-6 weeks ▪ Vancomycin plus streptomycin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Strains resistant to penicillin and susceptible to aminoglycosides and vancomycin: ▪ β-lactamase–producing strain: • Ampicillin-sulbactam plus gentamicin for 6 weeks

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	• Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for 6 weeks o Strains resistant to penicillin, aminoglycosides and vancomycin: ▪ *E. faecium*: linezolid or quinupristin-dalfopristin for at least 8 weeks ▪ *E. faecalis*: imipenem/cilastatin plus ampicillin or ceftriaxone plus ampicillin for at least 8 weeks • Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin-sulbactam or ciprofloxacin for 4-6 weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin, gatifloxacin, or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin for 4-6 weeks ▪ Vancomycin plus gentamicin plus ciprofloxacin for 4-6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillins) o Prosthetic valve (early, <1 year): ▪ Vancomycin (for 6 weeks) plus gentamicin (for 2 weeks) plus cefepime (for 6 weeks) plus rifampin (for 6 weeks) o Prosthetic valve (late, ≥1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone (for 6 weeks) plus gentamicin (for 2 weeks) with or without doxycycline (for 6 weeks) ▪ Documented *Bartonella*, culture positive: • Doxycycline (for 6 weeks) plus gentamicin for (2 weeks)
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines: Management of Encephalitis[81] (2008)**	Empirical Therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or trimethoprim-sulfamethoxazole is recommended • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; trimethoprim-sulfamethoxazole is an alternative in the penicillin-

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	allergic patient • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered • *Tropheryma whipplei:* ceftriaxone, followed by either trimethoprim-sulfamethoxazole or cefixime, is recommended Rickettsioses and Ehrlichioses • *Anaplasma phagocytophilum:* doxycycline is recommended • *Ehrlichia chaffeensis:* doxycycline is recommended • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative Protozoa • *Acanthamoeba:* trimethoprim-sulfamethoxazole plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; trimethoprim-sulfamethoxazole alone and pyrimethamine plus either atovaquone, clarithromycin, azithromycin, or dapsone are alternatives • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections[20] (2005)**	Overview
	• Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first- or second-generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of methicillin-resistant S*taphylococcus aureus* (MRSA) strains.
	Animal Bites
	• Oral treatment options
	  o Amoxicillin/clavulanate is recommended.
	  o Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin.
	  o Other options, including fluoroquinolones, trimethoprim-sulfamethoxazole, and cefuroxime, may require an additional agent active against anaerobes, such as metronidazole or clindamycin.
	  o First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro

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	activity against *P. multocida* and should be avoided. Soft-tissue Infections Caused by Community-Acquired MRSA • They are often susceptible to non-β-lactam antibiotics, and standard treatment includes doxycycline, clindamycin, trimethoprim-sulfamethoxazole, rifampin, or fluoroquinolones, specifically levofloxacin, gatifloxacin or moxifloxacin.
World Gastroenterology Organization (WGO): **Acute Diarrhea**[84] **(2008)**	General Considerations • Antimicrobials are the drugs of choice for empirical treatment of traveler's diarrhea and of community-acquired secretory diarrhea when the pathogen is known. • Consider antimicrobial treatment for: o Persistent *Shigella*, *Salmonella*, *Campylobacter*, or parasitic infections o Infections in the aged, immunocompromised patients, and patients with impaired resistance, sepsis, or with prostheses o Moderate/severe traveler's diarrhea or diarrhea with fever and/or with bloody stools (quinolones as initial therapy or co-trimoxazole as a second choice) • Nitazoxanide may be appropriate for *Cryptosporidium* and other infections, including some bacteria. • Rifaximin may also be useful. Antimicrobial Agents for the Treatment of Specific Causes of Diarrhea • Cholera o First-line: doxycycline or tetracycline o Alternative: azithromycin or ciprofloxacin • Shigellosis o First-line: ciprofloxacin o Alternative: pivmecillinam or ceftriaxone • Amebiasis o First-line: metronidazole • Giardiasis o First-line: metronidazole • *Campylobacter* o First-line: azithromycin
Infectious Diseases Society of America (IDSA): **The Practice of Travel Medicine**[83] **(2006)**	Chemoprophylaxis • Bismuth subsalicylate–containing formulations and antibiotics have been proven effective in preventing traveler's diarrhea. • Probiotics, such as lactobacillus, have not demonstrated sufficient efficacy to be recommended. • Widespread drug resistance renders doxycycline and trimethoprim-sulfamethoxazole (TMP-SMX) no longer useful for prevention of traveler's diarrhea. • Chemoprophylaxis can contribute to development of resistant enteric bacteria and potentially predispose the traveler to infection with other deleterious pathogens, such as *Clostridium difficile.* • The routine use of antibiotic prophylaxis for travelers' diarrhea is not generally recommended. • Chemoprophylaxis may be considered in healthy travelers for whom staying well is critical and in special-needs travelers in whom the risk for diarrhea is increased or the consequences of a diarrheal episode may be severe. • When considering chemoprophylaxis, fluoroquinolone antibiotics remain the first choice. • Chemoprophylaxis should be recommended for no more than 2–3

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	weeks. Treatment • Fluid replacement and a diet restricted to liquids and bland foods may be appropriate, though they may not provide additional benefits beyond antibiotic treatment. • Symptomatic therapy with bismuth subsalicylate may be recommended in mild cases of diarrhea, but better agents exist for moderate-to-severe disease. • Loperamide has become the antimotility agent of choice. It is more efficacious in controlling diarrhea than bismuth subsalicylate and has an onset of action within the first 4 hours after ingestion. When it is used in combination with an antibiotic, there may be rapid improvement of traveler's diarrhea. • Antibiotics are effective in the treatment of traveler's diarrhea and can reduce the average duration of disease from several days to ~1 day. • Antibiotics that are recommended include fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin, levofloxacin), azithromycin, and rifaximin. • Fluoroquinolones remain predictably active for empiric therapy in most parts of the world and remain the drugs of first choice. • Antibiotics that are no longer recommended because of drug resistance worldwide are the sulfonamides, neomycin, ampicillin, doxycycline, tetracycline, trimethoprim alone, and TMP-SMX.

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Infectious Diarrhea[82] (2001)**	Recommendations for Therapy Against Specific Pathogens
	• *Shigella* species:
	  o Trimethoprim-sulfamethoxazole (TMP-SMZ)
	  o Fluoroquinolone
	  o Nalidixic acid
	  o Ceftriaxone
	  o Azithromycin
	• *Salmonella,* non-typhi species:
	  o Treament is not routinely recommended; however, consider therapy in patients <6 months old or >50 years old, or patients that have a prosthesis, valvular heart disease, severe atherosclerosis, malignancy, or uremia.
	  o TMP-SMZ
	  o Fluoroquinolone
	• *Campylobacter* species
	  o Erythromycin
	• *Escherichia coli* species
	  o TMP-SMZ
	  o Fluoroquinolone
	• *Aeromonas* or *Plesiomonas* species
	  o TMP-SMZ
	  o Fluoroquinolone
	• *Yersinia* species
	  o Antibiotic therapy is not usually required. For severe infections or associated bacteremia, combination therapy with doxycycline, aminoglycosides TMP-SMZ or a fluoroquinolone is recommended.
	• *Vibrio cholerae*
	  o Doxycycline or tetracycline
	  o Fluoroquinolone
	• Toxigenic *Clostridium difficile*
	  o Metronidazole

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	• *Isospora* species
	  o TMP-SMZ
	• *Cyclospora* species
	  o TMP-SMZ

American College of Gastroenterology (ACG): **Guideline on the Management of *Helicobacter pylori* Infection**[21] **(2007)**	• The recommended primary therapies for *H. pylori* infection include: a PPI, clarithromycin, and amoxicillin, or metronidazole (clarithromycin-based triple therapy) for 14 days or a PPI or H2RA, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10–14 days.
Canadian Helicobacter Study Group Consensus Conference: **Update on the Management of *Helicobacter pylori***[22] **(2004)**	• A quadruple combination of a PPI, bismuth, tetracycline, and metronidazole for 10-14 days can be considered first-line therapy for the eradication of *H. pylori.* • Eradication rates with the recommended quadruple therapy are comparable with those achieved with PPI-based triple therapy regimens in patients who adhere to the protocol. Given the lower number of tablets and twice daily dosing, in practice, PPI-based triple therapy may be the first choice.
European *Helicobacter pylori* Study Group: **Current Concepts in the Management of *H. pylori* Infection–The Maastricht 2-2000 Consensus Report**[23] **(2002)**	• First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole. • Second-line therapy should use quadruple therapy with a PPI, bismuth, metronidazole, and tetracycline. • When bismuth is not available, second-line therapy should be triple therapy with a proton-pump inhibitor.
Canadian Dyspepsia Working Group: **An Evidence-Based Approach to the Management of Uninvestigated Dyspepsia in the Era of *Helicobacter pylori***[24] **(2000)**	• First-line eradication therapies for *H. pylori* are triple therapies of a PPI plus amoxicillin plus clarithromycin (PPI + AC), or a PPI plus metronidazole plus clarithromycin (PPI + MC), twice daily for 1 week; or ranitidine bismuth citrate plus either AC or MC. • If the first eradication therapy has failed, the action recommended by the Canadian *Helicobacter pylori* Consensus Conference is to use a different first-line therapy than that used initially (e.g., switch from PPI + AC to PPI + MC). • An alternative therapy is a 14-day quadruple regimen of a PPI (twice daily) plus bismuth (subsalicylate, 2 tablets 4 times daily) plus metronidazole (250 mg 4 times daily) plus tetracycline (500 mg 4 times daily) (PPI + BMT). • For the management of patients negative for *H. pylori*, a PPI is the first-line therapy choice.

Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines**[27] **(2010)**	<u>Granuloma Inguinale (Donovanosis)</u>
	• Recommended regimen:
	  o Doxycycline 100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed
	• Alternative regimens:
	  o Azithromycin 1 g orally once per week for at least 3 weeks and until all lesions have completely healed
	  o Ciprofloxacin 750 mg orally twice a day for at least 3 weeks and until all lesions have completely healed
	  o Erythromycin base 500 mg orally four times a day for at least 3 weeks and until all lesions have completely healed
	  o Trimethoprim-sulfamethoxazole one double-strength (160 mg/800 mg) tablet orally twice a day for at least 3 weeks and until all lesions have completely healed
	• The addition of an aminoglycoside (e.g., gentamicin 1 mg/kg IV every 8 hours) to these regimens can be considered if improvement is not

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	evident within the first few days of therapy. Lymphogranuloma Venereum • Recommended regimen: o Doxycycline 100 mg orally twice a day for 21 days • Alternative regimen: o Erythromycin base 500 mg orally four times a day for 21 days Nongonococcal Urethritis • Recommended regimens: o Azithromycin 1 g orally in a single dose o Doxycycline 100 mg orally twice a day for 7 days • Alternative regimens: o Erythromycin base 500 mg orally four times a day for 7 days o Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days o Levofloxacin 500 mg orally once daily for 7 days o Ofloxacin 300 mg orally twice a day for 7 days Cervicitis • Recommended regimens for presumptive treatment: o Azithromycin 1 g orally in a single dose o Doxycycline 100 mg orally twice a day for 7 days Chlamydial Infections • Recommended regimens: o Azithromycin 1 g orally in a single dose o Doxycycline 100 mg orally twice a day for 7 days • Alternative regimens: o Erythromycin base 500 mg orally four times a day for 7 days o Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days o Levofloxacin 500 mg orally once daily for 7 days o Ofloxacin 300 mg orally twice a day for 7 days Chlamydial Infections Among Children • Recommended regimen for children <45 kg: o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days • Recommended regimen for children ≥45 kg and <8 years of age: o Azithromycin 1 g orally in a single dose • Recommended regimens for children ≥8 years of age: o Azithromycin 1 g orally in a single dose o Doxycycline 100 mg orally twice a day for 7 days Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum • Recommended regimens: o Ceftriaxone 250 mg IM in a single dose o Cefixime 400 mg orally in a single dose o Single-dose injectable cephalosporin regimens plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for 7 days Uncomplicated Gonococcal Infections of the Pharynx • Recommended regimens: o Ceftriaxone 250 mg IM in a single dose plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for 7 days Pelvic Inflammatory Disease • Recommended parenteral regimen A: o Cefotetan 2 g IV every 12 hours o Cefoxitin 2 g IV every 6 hours plus doxycycline 100 mg

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	orally or IV every 12 hours
	• Recommended parenteral regimen B:
	  o Clindamycin 900 mg IV every 8 hours plus gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) can be substituted.
	• Alternative parenteral regimens:
	  o Ampicillin/Sulbactam 3 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours
	• Recommended oral regimen:
	  o Ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
	  o Cefoxitin 2 g IM in a single dose and probenecid, 1 g orally administered concurrently in a single dose, plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
	  o Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
	<u>Epididymitis</u>
	• Recommended regimens :
	  o Ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg orally twice a day for 10 days
	• For acute epididymitis most likely caused by enteric organisms:
	  o Levofloxacin 500 mg orally once daily for 10 days
	  o Ofloxacin 300 mg orally twice a day for 10 days
	<u>Proctitis, Proctocolitis, and Enteritis</u>
	• Recommended regimen:
	  o Ceftriaxone 250 mg IM plus doxycycline 100 mg orally twice a day for 7 days

Working Group on Civilian Biodefense: **Anthrax as a Biological Weapon, Updated Recommendations for Management**[32] **(2002)**	<u>Inhalation Anthrax in the Contained Casualty Setting - Adults</u> • Ciprofloxacin 400 mg IV every 12 hours initially, then 500 mg by mouth twice daily when clinically appropriate OR • Doxycycline 100 mg IV every 12 hours initially with either one or two of the following: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and/or clarithromycin. Switch to 100 mg by mouth twice daily when clinically appropriate. <u>Inhalation Anthrax in the Contained Casualty Setting - Children</u> • Ciprofloxacin 10-15 mg/kg every 12 hours IV, then 10-15 mg/kg by mouth every 12 hours when clinically appropriate OR • Doxycycline (if ≤45 kg–2.2 mg/kg IV; if > 45 kg–100 mg IV) every 12 hours initially with either one or two of the following: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and/or clarithromycin. Switch to oral therapy when clinically appropriate using same IV dose. <u>Inhalation Anthrax in a Mass Casualty Setting - Adults</u> • Recommended treatment: ciprofloxacin 500 mg by mouth every 12 hours • Alternative treatment option: doxycycline 100 mg by mouth every 12 hours or amoxicillin 500 mg by mouth every 8 hours <u>Inhalation Anthrax in a Mass Casualty Setting - Children</u> • Recommended treatment: ciprofloxacin 10-15 mg/kg by mouth every 12 hours

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	• Alternative treatment option: amoxicillin 500 mg by mouth every 8 hours (weight ≥20 kg) or amoxicillin 40 mg/kg by mouth every 8 hours (weight <20 kg) <u>Inhalation Anthrax in a Mass Casualty Setting – Pregnant Women</u> • Recommended treatment: ciprofloxacin 500 mg by mouth every 12 hours • Alternative treatment option: amoxicillin 500 mg by mouth every 8 hours <u>Cutaneous Anthrax Infection Associated with a Bioterrorism Attack - Adults</u> • Ciprofloxacin 500 mg by mouth every 12 hours OR • Doxycycline 100 mg by mouth every 12 hours <u>Cutaneous Anthrax Infection Associated with a Bioterrorism Attack - Children</u> • Ciprofloxacin 10-15 mg/kg by mouth every 12 hours OR • Doxycycline 2.2 mg/kg (weight ≤45 kg) or 100 mg (weight >45 kg) by mouth every 12 hours

Global Initiative for Chronic Obstructive Lung Disease (GOLD): **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[28] (2010)**	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in COPD.
	• There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful.
	• Based on current available evidence, antibiotics should be given to:
	  o Patients with exacerbations of COPD with the following three cardinal symptoms: dyspnea, sputum volume, and sputum purulence.
	  o Patients with exacerbations of COPD with two of the cardinal symptoms, if the increased purulence of sputum is one of the two symptoms.
	  o Patients with a severe exacerbation of COPD that requires mechanical ventilation (invasive or noninvasive).
	• Antibiotic treatment in exacerbations of COPD:
	  o Group A (mild exacerbation; no risk factors for poor outcome)
	  ▪ Recommended oral treatment: β-lactam (penicillin, ampicillin, amoxicillin), tetracycline, or trimethoprim-sulfamethoxazole
	  ▪ Alternative oral treatment: β-lactam/β-lactamase inhibitor, macrolides, second or third generation cephalosporin, or ketolides
	  o Group B (moderate exacerbation with risk factor(s) for poor outcome)
	  ▪ Recommended oral treatment: β-lactam/β-lactamase inhibitor
	  ▪ Alternative oral treatment: fluoroquinolones (gemifloxacin, levofloxacin, moxifloxacin)
	  ▪ Parenteral treatment: β-lactam/β-lactamase inhibitor, second or third generation cephalosporin, or fluoroquinolones (levofloxacin, moxifloxacin)
	  o Group C (severe exacerbation with risk factors for *P. aeruginosa* infection)
	  ▪ Recommended oral treatment: fluoroquinolones (ciprofloxacin, levofloxacin)
	  ▪ Parenteral treatment: fluoroquinolones (ciprofloxacin, levofloxacin) or β-lactam with *P.*

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	aeruginosa activity

Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS): **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults[29] (2007)**	<u>Empirical Antimicrobial Therapy</u>
	• Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.
	• Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.
	• Outpatient treatment
	  o Previously healthy and no risk factors for drug-resistant *S. pneumoniae* (DRSP) infection:
	  ▪ Macrolide (azithromycin, clarithromycin, or erythromycin)
	  ▪ Doxycycline
	  o Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected); or other risks for DRSP infection:
	  ▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin)
	  ▪ β-lactam plus a macrolide (High-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide.)
	  o In regions with a high rate of infection with high-level macrolide-resistant *S. pneumoniae,* consider the use of alternative agents listed above for any patient, including those without comorbidities.
	• Inpatient, non-ICU treatment
	  o Respiratory fluoroquinolone
	  o β-lactam plus a macrolide (Preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients).
	• Inpatient, ICU treatment
	  o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended.)
	  o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam).
	  o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.

American College of Chest Physicians (ACCP):	• Antibiotic choice and route of administration are central to an appropriate in-home treatment plan. The oral route is recommended if

Clinical Guideline	Recommendation(s)
Management of Community-Acquired Pneumonia in the Home: An American College of Chest Physicians Clinical Position Statement[30] (2005)	the patient can tolerate it, and if the availability and activity of the agent are adequate. • Although treatment is facilitated if the etiologic agent is known (pathogen-directed treatment for CAP is provided in the IDSA guidelines), most outpatient treatment is empiric. • The use of a macrolide, doxycycline, or fluoroquinolone agent, as recommended both by the IDSA and the ATS guidelines, may be appropriate empiric outpatient treatment for low-risk patients (i.e., otherwise young healthy individuals). Alternatives to these agents in low-risk patients are amoxicillin/clavulanate and some second-generation cephalosporins (e.g., cefuroxime, cefpodoxime, or cefprozil). • A lack of response to treatment with macrolides and fluoroquinolones has been reported. Some authorities prefer to reserve the use of fluoroquinolones for older patients, patients who are allergic or intolerant to macrolides, patients who have recently received macrolide treatment, patients with comorbidities, patients with documented infections with highly resistant pneumococci, or patients with a lack of response to treatment with another agent. • The IDSA and ATS recommendations generally agree that a patient who is at high risk either because of complicated comorbidities or extensive prior antibiotic use may be a candidate for treatment with either a β-lactam/macrolide combination or a antipneumococcal fluoroquinolone. • Double therapy with either a β-lactam/macrolide combination or a β-lactam/ antipneumococcal fluoroquinolone should be considered in patients who would normally be considered for ICU admission but have chosen to remain in the home.
Infectious Diseases Society of America (IDSA): **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children[34] (2010)**	<u>Community-Acquired Infection in Adults: Mild to Moderate Severity</u> • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*E. Coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. <u>Community-Acquired Infection in Adults: High Severity</u> • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or

Clinical Guideline	Recommendation(s)
	ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *E. coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E. coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended. • Use of agents effective against MRSA or yeast is not recommended in the absence of evidence of infection due to such organisms. <u>Community-Acquired Infection in Pediatric Patients:</u> • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected MRSA or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. <u>Health Care-Associated Infection:</u> • Therapy should be based on microbiologic results. To achieve empiric coverage, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. <u>Cholecystitis and Cholangitis:</u> • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.
Infectious Diseases Society of America (IDSA): **The Clinical**	• Doxycycline, amoxicillin or cefuroxime axetil for 14 days is recommended for the treatment of adult patients with early localized or

Clinical Guideline	Recommendation(s)
Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis[33] (2006)	early disseminated Lyme disease associated with erythema migrans, in the absence of specific neurologic manifestations (see Lyme meningitis, below) or advanced atrioventricular heart block. • Each of these antimicrobial agents has been shown to be highly effective for the treatment of erythema migrans and associated symptoms in prospective studies. • Doxycycline has the advantage of being effective for treatment of HGA (but not for babesiosis), which may occur simultaneously with early Lyme disease. • First-generation cephalosporins, such as cephalexin, are ineffective for treatment of Lyme disease and should not be used. • Ceftriaxone is not superior to oral agents and is more likely than the recommended orally administered antimicrobials to cause serious adverse effects. Therefore, ceftriaxone is not recommended for treatment of patients with early Lyme disease in the absence of neurologic involvement or advanced atrioventricular heart block.
Infectious Diseases Society of America (IDSA): **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus*[25] (2011)**	Skin and Soft-Tissue Infections (SSTIs) • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired (CA) MRSA is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for CA-MRSA is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of CA-MRSA in outpatients with SSTI, oral antibiotic options include the following: clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and CA-MRSA is desired, options include the following: clindamycin alone or TMP-SMX or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of SSTIs is not recommended. • For hospitalized patients with complicated SSTIs, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for MRSA should be considered pending culture data. Options include the following: vancomycin intravenous (IV), linezolid oral (PO) or IV, daptomycin IV, telavancin IV, and clindamycin IV or PO. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to MRSA-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and

Clinical Guideline	Recommendation(s)
	secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with cSSTIs, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin IV is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative. <u>MRSA Bacteremia and Infective Endocarditis (Native Valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin IV for at least 2 weeks is recommended. For complicated bacteremia, 4–6 weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, IV vancomycin or daptomycin for 6 weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>MRSA Bacteremia and Infective Endocarditis (Prosthetic Valve)</u> • IV vancomycin plus rifampin PO/IV for at least 6 weeks plus gentamicin IV for 2 weeks. • In children, vancomycin IV is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from 2 to 6 weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin IV may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. <u>Management of MRSA Pneumonia</u> • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for MRSA is recommended pending sputum and/or blood culture results. • For health care–associated MRSA (HA-MRSA) or CA-MRSA pneumonia, IV vancomycin or linezolid PO/IV or clindamycin PO/IV, if the strain is susceptible, is recommended for 7–21 days, depending on the extent of infection. • In children, IV vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin IV can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative. <u>Management of MRSA Bone and Joint Infections</u> • Antibiotics available for parenteral administration include IV vancomycin and daptomycin. • Some antibiotic options with parenteral and oral routes of administration include the following: TMP-SMX in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia. • A minimum 8-week course is recommended. Some experts suggest an

Clinical Guideline	Recommendation(s)

	additional 1–3 months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with TMP-SMX, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities.
	• For septic arthritis, refer to antibiotic choices for osteomyelitis. A 3 to 4-week course of therapy is suggested.
	<u>Management of MRSA Infections of the CNS</u>
	• Meningitis
	  o IV vancomycin for 2 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid or TMP-SMX.
	  o For CNS shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid (CSF) cultures are repeatedly negative.
	• Brain abscess, subdural empyema, spinal epidural abscess
	  o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and TMP-SMX.
	• Septic thrombosis of cavernous or dural venous sinus
	  o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and TMP-SMX.
	  o IV vancomycin is recommended in children.

Working Group on Civilian Biodefense (WGCB): **Plague as a Biological Weapon: Medical and Public Health Management Consensus Statement[31] (2000)**	• For adults with pneumonic plague in the contained casualty settings, the preferred choice is streptomycin or gentamicin and alternative choices include doxycycline, ciprofloxacin, or chloramphenicol. • For children with pneumonic plague in the contained casualty settings, the preferred choice is streptomycin or gentamicin and alternative choices include doxycycline, ciprofloxacin, or chloramphenicol. • For pregnant women with pneumonic plague in the contained casualty settings, the preferred choice is gentamicin and an alternative choice is doxycycline. • For adults with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline, or ciprofloxacin and the alternative choice is chloramphenicol. • For children with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin and an alternative choice is chloramphenicol. • For pregnant women with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin and an alternative choice is chloramphenicol.
Centers for Disease Control and Prevention (CDC): **Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichioses, and Anaplasmosis—United States[26] (2006)**	• The CDC recommends doxycycline as the treatment of choice for all tickborne rickettsial diseases in children and adults. • Chloramphenicol is an alternative drug that has been used to treat Rocky Mountain spotted fever (RMSF); however, it is associated with various side effects and might require monitoring of blood indices. • Epidemiologic studies in which CDC case report data have been used suggested that patients with RMSF treated with chloramphenicol have a higher risk of dying than persons who received a tetracycline.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the tetracyclines are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Tetracyclines[1-8]

Indication	Demeclocycline	Doxycycline	Minocycline	Oxytetracycline	Tetracycline	Tigecycline
Central Nervous System Infections						
Treatment of asymptomatic meningococcal carriers			✔			
Dermatological Infections						
Acne	✔	✔	✔		✔	
Rosacea		✔				
Skin and skin-structure infections	✔	✔	✔	✔	✔	✔
Yaws	✔	✔	✔		✔	
Gastrointestinal Infections						
Cholera	✔	✔	✔		✔	
Intestinal amebiasis	✔	✔	✔	✔	✔	
Peptic ulcers caused by *H. Pylori*					✔	
Genitourinary Infections						
Chancroid	✔	✔	✔	✔	✔	
Chlamydial infection		✔	✔		✔	
Epididymitis		✔				
Granuloma inguinale	✔	✔	✔	✔	✔	
Syphilis	✔	✔	✔	✔	✔	
Urethritis (gonococcal)	✔					
Urethritis/cervicitis (gonococcal)		✔	✔	✔	✔	
Urethritis (non-gonococcal)	✔					
Urethritis/cervicitis (non-gonococcal)		✔	✔		✔	
Urinary tract infections	✔	✔	✔	✔	✔	
Respiratory Infections						
Anthrax	✔	✔	✔	✔	✔	
Mycoplasma pneumonia		✔	✔		✔	
Pneumonia (community-acquired)						✔
Respiratory tract infections	✔	✔	✔	✔	✔	
Miscellaneous Infections						
Actinomycotic infections	✔	✔	✔		✔	
Bartonellosis	✔	✔	✔		✔	

Indication	Demeclocycline	Doxycycline	Minocycline	Oxytetracycline	Tetracycline	Tigecycline
Brucellosis	✔	✔	✔		✔	
Campylobacter fetus infections	✔					
Clostridial infections	✔	✔	✔		✔	
Disease caused by rickettsiae	✔	✔	✔	✔	✔	
Inclusion conjunctivitis	✔	✔	✔		✔	
Intra-abdominal infections						✔
Listeriosis	✔	✔	✔		✔	
Lymphogranuloma venereum	✔	✔	✔	✔	✔	
Malaria prophylaxis		✔				
Ornithosis				✔		
Periodontitis			✔		✔	
Plague	✔	✔	✔		✔	
Psittacosis	✔	✔	✔	✔	✔	
Q fever	✔	✔	✔	✔	✔	
Relapsing fever	✔	✔	✔	✔	✔	
Rocky Mountain spotted fever	✔	✔	✔	✔	✔	
Shigellosis		✔	✔		✔	
Spotted fevers		✔	✔		✔	
Trachoma	✔	✔	✔		✔	
Tularemia	✔	✔	✔		✔	
Typhus	✔	✔	✔	✔	✔	
Vincent’s infection	✔	✔	✔		✔	

IV. Pharmacokinetics

The pharmacokinetic parameters of the tetracyclines are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Tetracyclines[1-8]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Demeclocycline	50-80	40-90	Liver	Renal (44) Feces (13-46)	10-16
Doxycycline	100	80-93	Liver (50)	Renal (40)	18-22
Minocycline	90	76	Not reported	Renal (10-13)	11-22
Oxytetracycline	75	27-35	Liver	Renal (60-70)	8.5-9.6
Tetracycline	75	65	Liver	Renal (60)	8-11
Tigecycline	Not reported	71-89	Liver	Renal (33) Feces (59)	42

V. Drug Interactions

Significant drug interactions with the tetracyclines are listed in Table 6.

Table 6. Significant Drug Interactions with the Tetracyclines[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Tetracyclines	1	Acitretin	Acitretin may increase the risk of pseudotumor cerebri. An additive adverse effect is thought to be responsible. Avoid concomitant and subsequent monotherapy usage of these agents.
Tetracyclines	1	Anticoagulants	The action of oral anticoagulants may be increased because of the elimination of vitamin K-producing gut bacteria by tetracyclines.
Tetracyclines	1	Isotretinoin	Isotretinoin may increase the risk of pseudotumor cerebri. An additive adverse effect is thought to be responsible. Avoid concomitant and subsequent monotherapy usage of these agents.
Doxycycline	2	Barbiturates	Barbiturates increase the hepatic metabolism of doxycycline, which decreases the half-life and serum levels.
Doxycycline	2	Carbamazepine	Carbamazepine may decrease the half-life and serum levels of doxycycline due to increased hepatic metabolism.
Doxycycline	2	Hydantoins	Induction of hepatic microsomal enzymes by hydantoins may increase the metabolic elimination of doxycycline.
Tetracyclines	2	Antacids	Tetracyclines administered with aluminum, calcium, magnesium, iron, or zinc salts form an insoluble chelate, thereby decreasing the absorption and serum levels of the

Generic Name(s)	Significance Level	Interaction	Mechanism
			tetracycline. Administer tetracyclines at least 2 hours before or after these agents.
Tetracyclines	2	Atovaquone	Reduced oral absorption of atovaquone may occur due to a disruption of the gastrointestinal tract caused by tetracyclines.
Tetracyclines	2	Bismuth salts	Co-administration of bismuth salts in liquid formulations may decrease the serum levels of tetracyclines. Give the bismuth salt 2 hours after the tetracycline.
Tetracyclines	2	Contraceptives	Tetracyclines may interfere with the enterohepatic recirculation of certain contraceptive steroids, leading to reduced efficacy. Although infrequently reported, contraceptive failure is possible.
Tetracyclines	2	Digoxin	Co-administration may result in increased serum levels of digoxin in a small subset of patients (10%). Monitor digoxin levels and signs of toxicity.
Tetracyclines	2	Methoxyflurane	Co-administration may enhance the risk for renal toxicity; deaths have been reported. Do not co-administer. If possible seek alternative agents.
Tetracyclines	2	Penicillins	The bacteriostatic action of tetracyclines may interfere with the bactericidal activity of penicillins. Consider avoiding this combination if at all possible.
Tetracyclines	2	Urinary alkalinizers	Co-administration may result in increased excretion of the tetracyclines and decreased serum levels. Separate administration by 3 to 4 hours; however, this may not be effective and an increase in tetracycline dose may be necessary if the pH of the urine remains increased.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the tetracyclines are noted in Table 7. The use of tetracyclines during the period of tooth development (from the last half of pregnancy through 8 years of age) may cause permanent discoloration of teeth. Due to the risk of this discoloration, the tetracyclines should not be used in children under eight years of age (except for the treatment and postexposure prophylaxis of anthrax), unless other drugs are not likely to be effective or are contraindicated. This adverse reaction is more common during long-term use of the drugs, but has been observed following repeated short-term courses.

Table 7. Adverse Drug Events (%) Reported with the Tetracyclines[1-8]

Adverse Events	Demeclocycline	Doxycycline	Minocycline	Oxytetracycline	Tetracycline	Tigecycline
Cardiovascular						
Bradycardia	-	-	-	-	-	✔
Pericarditis	✔	✔	✔	✔	✔	-
Central Nervous System						
Bulging fontanels	✔	✔	✔	✔	✔	-
Dizziness	✔	-	-	-	-	3
Fever	-	-	-	-	✔	-
Headache	✔	-	✔	-	-	6
Intracranial hypertension	-	✔	✔	✔	-	-
Intracranial pressure increased	-	-	-	-	✔	-
Pseudotumor cerebri	✔	-	✔	-	✔	✔
Dermatological						
Erythema multiforme	✔	✔	✔	-	-	-
Erythematous rash	✔	✔	✔	✔	✔	-
Exfoliative dermatitis	-	✔	✔	✔	✔	-
Maculopapular rash	✔	✔	✔	✔	✔	-
Nail discoloration	-	-	-	-	✔	-
Oncolysis	-	-	-	-	✔	-
Photosensitivity	✔	✔	✔	✔	✔	✔
Pruritus	-	-	-	-	-	<2
Rash	-	-	-	-	✔	3
Skin hyperpigmentation	✔	-	✔	-	-	-
Stevens-Johnson syndrome	✔	✔	✔	-	-	✔
Toxic epidermal necrolysis	-	✔	✔	✔	-	-
Urticaria	✔	✔	✔	-	✔	-
Endocrine and Metabolic						
Diabetes insipidus syndrome	✔	-	-	-	-	-
Nephrogenic diabetes insipidus	✔	-	-	-	-	-
Thyroid dysfunction	✔	-	✔	-	-	-
Gastrointestinal						

Adverse Events	Demeclocycline	Doxycycline	Minocycline	Oxytetracycline	Tetracycline	Tigecycline
Abdominal pain	-	-	-	-	-	6
Anorexia	✔	✔	✔	-	✔	<2
Black hairy tongue	-	-	-	-	✔	-
Diarrhea	✔	✔	✔	✔	✔	12
Dyspepsia	-	-	-	-	✔	2
Dysphagia	✔	✔	✔	✔	✔	-
Enamel hypoplasia	-	-	-	-	✔	-
Enterocolitis	✔	✔	✔	✔	✔	-
Esophageal ulcerations	✔	✔	✔	-	✔	-
Esophagitis	-	✔	✔	-	✔	-
Glossitis	✔	✔	✔	✔	✔	-
Nausea	✔	✔	✔	✔	✔	25-35
Oral pigmentation	-	✔	-	-	-	-
Pancreatitis	✔	-	-	-	✔	✔
Tooth discoloration	✔	✔	✔	✔	✔	✔
Vomiting	✔	-	✔	✔	✔	18-20
Genitourinary						
Acute renal failure	✔	-	✔	-	✔	-
Anogenital inflammatory lesions	-	✔	-	✔	✔	-
Azotemia	-	-	-	-	✔	✔
Balanitis	✔	-	✔	-	-	-
Leukorrhea	-	-	-	-	-	<2
Monilial overgrowth	✔	-	✔	-	✔	<2
Renal damage	-	-	✔	-	✔	-
Vaginitis	-	-	-	-	-	<2
Hepatic						
Hepatic cholestasis	-	-	-	-	-	✔
Hepatic dysfunction	-	-	-	-	-	✔
Hepatic failure	✔	-	-	-	✔	✔
Hepatitis	✔	-	-	-	-	-
Hepatotoxicity	✔	-	✔	-	✔	-
Jaundice	-	-	-	-	-	<2
Hematologic						
Anemia	-	-	-	✔	-	5
Eosinophilia	✔	✔	✔	✔	✔	<2
Hemolytic anemia	✔	✔	✔	-	✔	-
Neutropenia	✔	✔	✔	✔	✔	-

Adverse Events	Demeclocycline	Doxycycline	Minocycline	Oxytetracycline	Tetracycline	Tigecycline
Porphyria	-	-	- ✔	-	-	-
Prothrombin time increased	-	-	-	-	-	<2
Thrombocytopenia	✔	✔	✔	✔	✔	<2
Thrombocytopenic purpura	-	-	-	-	✔	-
Thrombophlebitis	-	-	-	-	✔	<2
Laboratory Test Abnormalities						
Acidosis	-	-	-	-	-	✔
Alkaline phosphatase increase	-	-	-	-	-	3
Amylase increased	-	-	-	-	-	3
Bilirubinemia	-	-	-	-	-	2
BUN increased	✔	✔	✔	✔	✔	3
Creatinine increased	-	-	-	-	-	<2
Hyperphosphatemia	-	-	-	-	-	✔
Hypocalcemia	-	-	-	-	-	<2
Hypoglycemia	-	-	-	-	-	<2
Hyponatremia	-	-	-	-	-	2
Hypoproteinemia	-	-	-	-	-	5
Total bilirubin increased	-	-	-	-	-	✔
Transaminases increased	✔	-	-	-	-	4-5
Musculoskeletal						
Arthralgia	-	-	-	-	✔	-
Polyarthralgia	✔	-	✔	-	-	-
Respiratory						
Cough	-	-	-	-	-	4
Dyspnea	-	-	-	-	-	3
Pneumonia	-	-	-	-	-	2
Pulmonary infiltrates	✔	-	✔	-	-	-
Other						
Abnormal healing	-	-	-	-	-	3
Abscess	-	-	-	-	-	2
Allergic reaction	-	-	-	-	-	<2
Anaphylactoid purpura	✔	-	✔	-	✔	-
Anaphylaxis	✔	✔	✔	✔	✔	✔
Angioneurotic edema	✔	✔	✔	✔	✔	-
Chills	-	-	-	-	-	<2
Hypersensitivity reaction	-	-	✔	✔	✔	-
Infection	-	-	-	-	-	7

Adverse Events	Demeclocycline	Doxycycline	Minocycline	Oxytetracycline	Tetracycline	Tigecycline
Injection site reaction	-	-	-	-	-	<2
Lupus erythematosus exacerbation	✔	✔	✔	-	✔	-
Lupus-like syndrome	✔	-	✔	-	-	-
Myasthenic syndrome	✔	-	-	-	-	-
Phlebitis	-	-	-	-	-	3
Pruritus	-	-	-	-	-	<2
Septic shock	-	-	-	-	-	<2
Stools abnormal	-	-	-	-	-	<2
Superinfection	-	-	-	-	-	✔
Taste perversion	-	-	-	-	-	<2
Thyroid gland discoloration	✔	✔	✔	-	✔	-
Tinnitus	✔	✔	✔	-	-	-
Visual disturbances	✔	-	-	-	-	-

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the tetracyclines are listed in Table 8.

Table 8. Usual Dosing Regimens for the Tetracyclines[1-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Demeclocycline	Gonorrhea: Patients sensitive to penicillin: administer 600 mg as an initial dose, followed by 300 mg every 12 hours for 4 days (total of 3 g) Unspecified Infections: 150 mg four times daily or 300 mg twice daily; continue for 24 to 48 hours after symptoms and fever has subsided.	Unspecified Infections: >8 years of age: 7 to 13 mg/kg/day divided into 2 to 4 doses	Tablet: 150 mg 300 mg
Doxycycline	Epididymo-Orchitis: Oral: 100 mg twice daily for 7 days or 300 mg, followed in one hour by a second 300 mg dose Inhalational Anthrax (Post-Exposure): Oral: 100 mg twice daily for 60 days Malaria Prophylaxis: Oral: 100 mg daily, beginning 1 to 2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area. Nongonococcal Urethritis: Oral: 100 mg twice daily for at least 7 days Syphilis: Oral (DR): Early: 200 mg/day in divided doses for 14 days Late: 200 mg/day in divided doses for 28 days Oral (IR): Primary/secondary: 300 mg/day in divided doses for at least 10 days Unspecified Infections: Oral: 200 mg on the first day of treatment (administered 100 mg every 12 hours), followed by a	Inhalational Anthrax (Post-Exposure): Oral: <45 kg: 2.2 mg/kg every 12 hours for 60 days ≥45 kg: 100 mg twice daily for 60 days Malaria Prophylaxis: >8 years of age: Oral: 2.2 mg/kg daily, beginning 1 to 2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area. Unspecified Infections: >8 years of age: <45 kg: 4.4 mg/kg divided into two doses on the first day, followed by 2.2 mg/kg given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 4.4 mg/kg may be used. >45 kg: usual adult dose	Capsule: 50 mg 75 mg 100 mg 150 mg Injection: 100 mg Suspension: 25 mg/5 ml Syrup: 50 mg/5 ml Tablet: 50 mg 75 mg 100 mg 150 mg Tablet (DR): 75 mg 100 mg 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maintenance dose of 100 mg/day Urethral, Endocervical, or Rectal Infections: Oral: 100 mg twice daily for at least 7 days		
Minocycline	Gonococcal Infections: 200 mg initially, followed by 100 mg every 12 hours for a minimum of 4 days Gonococcal Urethritis (Men): 100 mg every 12 hours for 5days Meningococcal Carrier State: 100 mg every 12 hours for 5 days. *Mycobacterium Marinum* Infections: 100 mg every 12 hours for 6 to 8 weeks Syphilis: 200 mg initially, followed by 100 mg every 12 hours for 10 to 15 days Unspecified Infections: 200 mg initially, followed by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg capsules may be given initially followed by one 50 mg capsule four times daily. Urethral, Endocervical, or Rectal Infections: 100 mg every 12 hours for at least 7 days	Unspecified Infections: >8 years of age: 4 mg/kg initially, followed by 2 mg/kg every 12 hours	Capsule: 50 mg 75 mg 100 mg Tablet: 50 mg 75 mg 100 mg
Oxytetracycline	Unspecified Infections: 250 mg IM once every 24 hours or 300 mg/day divided every 8 to 12 hours	Unspecified Infections: >8 years of age: 15-25 mg/kg/day IM in divided doses every 8-12 hours	Injection: 100 mg/2 ml 250 mg/2 ml
Tetracycline	Acne: 1 gram daily in divided doses. Brucellosis: 500 mg four times daily for 3 weeks plus streptomycin 1 g IM twice daily the first week and once daily the second week Gonorrhea: 500 mg four times daily for 7	Unspecified Infections: >8 years of age: 25 to 50 mg/kg divided in four equal doses	Capsule: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	days Syphilis: Early: 500 mg four times daily for 15 days Late: 500 mg four times daily for 30 days Unspecified Infections: 500 mg twice daily or 250 mg four times daily		
Tigecycline	Intra-Abdominal Infections: 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours for 5 to 14 days Pneumonia (Community-Acquired): 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours for 7 to 14 days Skin and Skin-Structure Infections: 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours for 5 to 14 days Unspecified Infections: 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	Safety and efficacy in children have not been established.	Injection: 50 mg

DR=delayed-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the tetracyclines are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Tetracyclines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Cenizal et al.[62] (2007) Doxycycline100 mg twice daily for 7 days vs sulfamethoxazole-trimethoprim 160 mg/800 mg twice daily for 7 days	RCT, OL Patients with skin and soft-tissue infections (SSTI) presenting to an emergency room requiring wound packing without hospitalization	N=34 28 to 35 days	Primary: Clinical failure	Primary: Three clinical failures (21%) occurred in the trimethoprim-sulfamethoxazole group with no clinical failures in the doxycycline group. All three clinical failures were hospitalized due to worsening of the initial SSTI, which subsequently improved with no other complications. By intention-to-treat analysis, a comparison of the treatment groups showed there were no statistically significant differences in failure rates (P=0.283). Three patients in each treatment group required repeated outpatient incision and drainage at 2 to 5 days after enrollment. All other subjects reported good response at 10 to 14 days after initial presentation. Telephone follow-up at 28 to 35 days after initial presentation found that 21.4% subjects in the trimethoprim-sulfamethoxazole group and 17.6% of subjects in the doxycycline group had recurrent SSTI (all at new sites).
Teras et al.[57] (2008) Tigecycline 100 mg as initial dose, followed by 50 mg IV twice daily vs vancomycin 1 g IV twice daily plus aztreonam 2 g IV twice daily	RCT, DB, MC Patients with complicated skin and skin structure infections (cSSSIs)	N=546 14 days	Primary: Clinical response in the clinical modified intent-to-treat (c-mITT) and clinically evaluable populations at the test-of-cure (TOC) visit Secondary: Microbiologic response at the TOC visit and safety	Primary: The clinical responses in the tigecycline and the vancomycin/aztreonam groups in the clinically evaluable population were 89.8% vs 95.0%. The cure rates were similar in the c-mITT evaluation. This study subset was not powered for non-inferiority as was done in the full study set. Secondary: The microbiologic eradication rates at the test-of-cure visit were 84.8% and 93.2% for tigecycline and vancomycin/aztreonam, respectively. The number of patients reporting adverse events was similar in the two groups, with increased nausea and vomiting rates in the tigecycline group and an increased incidence of rash and increases in alanine aminotransferase and aspartate aminotransferase levels in the vancomycin/aztreonam group.
Chuang et al.[17]	DB, RCT, MC	N=127	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) Tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours (TGC) vs vancomycin 1 g IV plus aztreonam 2 g IV every 12 hours	Hospitalized patients ≥18 years of age with complicated skin and skin structure infections (cSSSIs)	5 to 14 days	Clinical response in clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) populations Secondary: Clinical response (cure or failure) by baseline isolate and type of infection	In India, the clinical response rates in the CE and c-mITT populations were higher in the TGC group than in the vancomycin-aztreonam group. CE rates were 83.3% in patients treated with TGC and 75.8% in patients treated with vancomycin-aztreonam. The c-mITT cure rates for TGC vs vancomycin-aztreonam were 78.6% vs 66.7%, respectively. Small sample size prevented non-inferiority analysis. In Taiwan, the clinical response rates in the CE populations were lower in the TGC group than in the vancomycin-aztreonam group. CE rates were 78.6% in patients treated with TGC and 90.0% in patients treated with vancomycin-aztreonam. The c-mITT cure rates for TGC vs vancomycin-aztreonam were 73.3% and 75%, respectively. Small sample size prevented any meaningful statistical analysis. Secondary: In India, the number of isolates was small and no definitive inferences are possible. However, TGC demonstrated antimicrobial efficacy against isolates commonly linked to cSSSIs, including *E. Faecalis, E. Coli, S. aureus and S. agalactiae*. No MRSA isolates were noted among Indian patients. In Taiwan, few isolates were available. They included one patient with MRSA, which responded to TGC.
Breedt et al.[51] (2005) Tigecycline 100 mg as an initial dose, then 50 mg IV every 12 hours for up to 14 days vs vancomycin 1 g IV BID and aztreonam 2 g IV BID for up	RCT, DB Patients with complicated skin and skin structure infections	N=546 92 days	Primary: Clinical response (improvement in drainage and/or discharge, fever, erythema, swelling, pain, and localized warmth) Secondary: Adverse events	Primary: The clinical responses in the tigecycline and the combination vancomycin and aztreonam groups were similar (84.3% vs 86.9%; P=0.4755). Microbiologic eradication (documented or presumed) occurred in 84.8% of the patients receiving tigecycline and 93.2% of the patients receiving vancomycin and aztreonam (P=0.0243). Secondary: The number of patients reporting adverse events was similar in the two groups, with increased nausea and vomiting rates in the tigecycline group and an increased incidence of rash and increases in alanine aminotransferase and aspartate aminotransferase levels in the combination vancomycin and aztreonam group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 14 days				
Gastrointestinal Infections				
Kearney et al.[65] (2000) Tetracycline 500 mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250 mg QID, and cimetidine 400 mg BID or famotidine 20 mg BID for 14 days (BMT-H_2) vs tetracycline 500 mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250 mg QID, and lansoprazole 30 mg BID for 7 days (BMT-PPI) vs metronidazole 500 mg BID, lansoprazole 30 mg BID, and clarithromycin 250 mg BID for 7 days (MLC)	OL Patients with peptic ulcer disease or prescribed H_2-receptor antagonists or PPIs, and who tested positive with histology, rapid urease or urea breath testing for *H pylori* infection	N=224 6 weeks	Primary: Defining treatment success rates for *H pylori* infection at end of study Secondary: Adverse events	Primary: The intent-to-treat cure rates for BMT-H_2, BMT-PPI, and MLC were 81%, 87%, and 90%, respectively (all, P>0.05). The per-protocol cure rates for BMT-H_2, BMT-PPI, and MLC were 84%, 91%, and 92% (all, P>0.05). Secondary: The side-effect profile for the 3 treatment groups revealed no significant differences in the frequency of the most common side effects, diarrhea and constipation. Metallic taste was significantly more severe in the MLC group (P=0.04). Nausea was significantly more common in the MLC group than the BMT-H_2 group (P=0.04). There were no significant differences in the frequency of dizziness/lightheadedness, cramping, or other side effects between the BMT-H_2 and MLC groups, and between BMT-PPI and BMT-H_2 groups. Severe headaches were significantly more frequent in the BMT-PPI group than the BMT-H_2 group (P=0.02). A significantly higher number of patients discontinued therapy due to adverse events in the BMT-H_2 and BMT-PPI treatment groups than the MLC group (P=0.049).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Magaret et al.[66] (2001) Tetracycline 250 mg QID, bismuth subsalicylate 2 tablets QID, lansoprazole 30 mg BID, and metronidazole 250 mg QID for 14 days vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days	RCT, MC Patients years of age failing prior treatment for *H pylori*	N=48 6 weeks	Primary: Negative ^{14}C-UBT of <50 dpm at time of follow-up indicating cure of infection Secondary: Side effects and compliance	Primary: Per-protocol eradication rates for patients on triple therapy and quadruple therapy were 82% and 80%, respectively (P=0.85). Intention-to-treat eradication rates for triple and quadruple therapy were 72% and 65%, respectively (P=0.63). Secondary: Compliance in patients receiving triple and quadruple therapy was 89% (P=0.98). Side effects were reported in 84% of patients on triple therapy and 82% of patients on quadruple therapy (P=0.85). Side effects included nausea (33%), upset stomach (25%), diarrhea (36%), abdominal pain (16%), lightheadedness/dizziness (4%), and fatigue (8%).
Miehlk et al.[67] (2003) Tetracycline 500 mg QID, bismuth citrate 107 mg QID, omeprazole 20 mg BID, and metronidazole 500 mg QID for 14 days vs omeprazole 40 mg QID and amoxicillin 750 mg QID for 14 days	RCT, XO Patients 18 to 80 years of age with at least one previous failure *of H pylori* therapy documented by confirmatory examinations and antimicrobial resistance to both metronidazole and clarithromycin	N=84 26 months	Primary: Two negative biopsy-based tests, histology and rapid urease test, or a validated ^{13}C-urea breath test to confirm successful treatment	Primary: In the per-protocol analysis, patients on high-dose dual therapy and quadruple therapy achieved *H pylori* cure rates of 83.8% and 92.1%, respectively (P=0.71). Cure rates using intent-to-treat analysis were 75.6% and 81.4% for high-dose dual therapy and quadruple therapy, respectively, and were not significantly different (P=0.60).
Perri et al.[68]	PRO, RCT, OL	N=135	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Tetracycline 500 mg QID, bismuth citrate 240 mg BID, pantoprazole 40 mg BID, and metronidazole 250 mg TID for 10 days (quadruple therapy group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 150 mg every other day for 10 days (RIF 150 mg group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 300 mg every other day for 10 days (RIF 300 mg group)	Patients with *H pylori* infection confirmed by ^{13}C-urea breath test after failure of one or more standard regimens	6 weeks	Eradication rates as defined by negative ^{13}C-urea breath test 4 weeks after end of treatment Secondary: Side effect rates reported after end of treatment	By intent-to-treat analysis, eradication rates for the pantoprazole, amoxicillin and rifabutin 150 mg treatment group (RIF 150 mg group) were 66.6%. Eradication rates for pantoprazole, metronidazole, bismuth citrate, and tetracycline (quadruple therapy group) were also 66.6%. The eradication rate for pantoprazole, amoxicillin, and rifabutin 300 mg (RIF 300 mg group) was 86.6%, which was significantly different than the other two treatment groups (P<0.025). Secondary: There was a significant difference in the side effects observed in rifabutin-treated patients compared to patients receiving quadruple therapy. The rates of side effects were 9%, 11% and 47%, (P<0.0001), for the triple therapies with the RIF 150 mg group, RIF 300 mg group, and quadruple therapy group, respectively.
Katelaris et al.[69] (2002) Tetracycline 500 mg QID, bismuth subcitrate 108 mg	RCT, MC, OL, PG Patients ≥18 years of age with *H pylori* infection confirmed by a positive urease	N=405 8 weeks	Primary: At week 8, ^{13}C-urea breath test to determine the outcome of eradication therapy	Primary: By intent-to-treat analysis, the eradication rates for the PAC7, PBTM7, and BTM14 treatment groups were 78%, 82% and 69%, respectively. By per-protocol analysis, the corresponding eradication rates were 82%, 88%, and 74%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QID, pantoprazole 40 mg BID, metronidazole 200 mg TID and 400 mg PM for 7 days (PBTM7) vs tetracycline 500 mg QID, bismuth subcitrate 108 mg QID, and metronidazole 200 mg TID and 400 mg PM for 14 days (BTM14) vs pantoprazole 40 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg BID (PAC7)	test and confirmatory histology and ^{13}C-urea breath test		Secondary: Compliance and adverse event profile	In both analysis, the eradication rates for PBTM7 and PAC7 were not significantly different (all P>0.05), while eradication rates for PBTM7 were significantly higher than BTM14 (P=0.01). Secondary: Adverse effects were common in all treatment groups. Adverse effects that interfered with activities of daily living were significantly higher in the BTM14 group (P<0.01). The number of patients who discontinued treatment due to adverse effects was also higher in the BTM14 group (9%) vs the PBTM7 group (3%) and the PAC7 group (2%). Noncompliance, defined as less than 90% of study drug taken, was higher in BTM14 than PBTM7 and PAC7.
Uygun et al.[70] (2007) Tetracycline 500 mg QID, bismuth subsalicylate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg TID (BLTM group)	RCT, SC, SB Patients with *H. pylori* infection and non-ulcer dyspepsia	N=240 14 days	Primary: *H. pylori* eradication rates	Primary: The ITT and PP populations, *H. pylori* eradication rates were 70% (95% CI, 61–78) and 82.3% (95% CI, 74–89) in the BLTM group, and 57.5% (95%CI 48–66) and 62.7% (95%CI 53–71) in the LAC group. The BLTM treatment achieved a significantly better eradication rate than the LAC treatment in PP analysis (82.3% vs 62.7%, P=0.002). Although a better ITT rate was obtained in the BLTM group than in the LAC group, the difference was not significant (70% vs 57.5%, P=0.06). Mild to severe side-effects, which were more frequent in the BLTM group,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs lansoprazole 30 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID (LAC)				were reported in 18.2% of the patients. Although it was not statistically significant, the number of patients ceasing the treatment for side-effects was more in BLTM group than in the LAC group.
Wu et al.[71] (2011) Tetracycline 500 mg QID, bismuth subcitrate 120 mg QID, esomeprazole 40 mg BID, and metronidazole for 7 days as rescue therapy (EBTM) vs tetracycline 500 mg QID, bismuth subcitrate120 mg QID, esomeprazole 40 mg BID, and amoxicillin 500 mg QID for 7 days as rescue therapy (EBTA)	RCT Patients ≥18 years of age with persistent *H. pylori* infection who failed standard first-line therapy (proton-pump inhibitor, clarithromycin and amoxicillin)	N=120 8 weeks posttreatment	Primary: Eradication rates, adverse events, resistance rates, compliance	Primary: In the ITT analysis, there was a significantly lower eradication rate for the EBTA group (62%; 95% CI, 50% to 75%) than for the EBTM group (81%; 95% CI, 71% to 91%; P=0.02). In the PP analysis, *H. pylori* infection was eradicated in 64% of the EBTA group (95% CI, 52% to 76%) and 83% of the EBTM group (95% CI, 74% to 92%; P=0.01). A total of 19% of patients in the EBTA group and 44% of patients in the EBTM group reported at least 1 adverse event during eradication therapy. The EBTA group had fewer adverse events than the EBTM group (P=0.004). The frequency of nausea in the EBTA group was lower than in the EBTM group (5% vs 16%, respectively). Tetracycline- and metronidazole-resistant strains were found in 2% and 53% of the patients, respectively. No strains developed resistance to amoxicillin. In the EBTA group, the *H. pylori* eradication rate for the tetracycline-susceptible strains was 67% by ITT analysis and 68% by PP analysis. All the strains in the subgroup were susceptible to amoxicillin. In the EBTM group, no tetracycline-resistant strains existed. The eradication rate of tetracycline-susceptible strains was 80% and 83% by ITT and PP analyses, respectively. With respect to metronidazole resistance, eradication rates were similar between susceptible and resistant strains by either ITT or PP analyses. Compliance rates were 97% in both treatment groups (P=1.00).
Songür et al.[72] (2009)	RCT, SC	N=464	Primary: Eradication rates,	Primary: In the per protocol analysis, eradication rates in LAC, BLTM, RBLTM,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tetracycline 500 mg QID, bismuth subcitrate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (BLTM) vs tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (RBLTM) vs tetracycline 500 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (LTM) vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500	Patients with *H. pylori* infection and dyspeptic symptoms	14 days	compliance	and LTM groups were 35.6%, 54.9%, 64.4%, and 60%, respectively. In the ITT analysis, eradication r rates in LAC, BLTM, RBLTM, and LTM groups were 32.7%, 47.1%, 57.3%, and 54.8%, respectively. The BLTM, RBLTM, and LTM treatment groups achieved a significantly better eradication rate than the LAC treatment group (P<0.001). There was no significant difference between BLTM, RBLTM, and LTM treatment groups. Compliance rates with LAC, BLTM, RBLTM, and LTM therapies were 91%, 87%, 90%, and 94%, respectively. The treatments were generally well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID for 14 days (LAC)				
Malfertheiner et al.[73] (2011) Tetracycline 125 mg, bismuth subcitrate potassium 140 mg, and metronidazole 125 mg (as a single three-in-one capsule) 3 capsules QID plus omeprazole 20 mg BID for 10 days (quadruple therapy) vs omeprazole 20 mg, amoxicillin 500 mg, and clarithromycin 500 mg BID for 7 days (standard therapy)	RCT, OL Patients ≥18 years of age with *H. pylori* infection and upper gastrointestinal symptoms	N=399 56 days posttreatment	Primary: Eradication rates, resistance rates, and safety	Primary: In the per protocol analysis, eradication rates were 93% with quadruple therapy compared to 70% with standard therapy (P<0.0001). Quadruple therapy was found to be non-inferior to standard therapy. In the intention-to-treat analysis, eradication rates were 80% with quadruple therapy compared to 55% with standard therapy (P<0.0001). Metronidazole sensitivity did not significantly affect the efficacy of quadruple therapy in the per protocol population (P=0.283). Clarithromycin sensitivity seemed to significantly affect the efficacy of standard therapy (P<0.0001). Simultaneous metronidazole and clarithromycin resistance reduced efficacy only in patients treated with standard therapy (P=0.001). The incidence of serious TEAEs and discontinuations due to a TEAE were similar between groups (<2.0%). The main adverse events were gastrointestinal and CNS disorders.
Zheng et al.[74] (2010) Tetracycline 750 mg BID, colloidal bismuth subcitrate 220 mg BID, pantoprazole 40 mg BID, and metronidazole 400	RCT, SC, OL Patients 18 to 70 years of age with non-ulcer dyspepsia (NUD) and *H. pylori* infection	N=170 7 to 10 days	Primary: Eradication rates, resistance rates, safety	Primary: In the ITT analysis, eradication rates were 63.5% in the PAC group and 89.4% in the PBMT groups (P<0.05). In the per protocol analysis, the eradication rates were 65.1% in the PAC group and 91.6% in the PBMT group (P<0.05). The *H. pylori* primary resistance rates to metronidazole and clarithromycin were 41.6% and 20.8%, respectively, whereas all the *H. pylori* isolates were sensitive to amoxicillin and tetracycline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg TID for 10 days (PBMT) vs pantoprazole 40 mg BID, amoxicillin 1.0 g BID and clarithromycin 500 mg BID for 7 days (PAC)				Adverse events were similar among the treatment groups and included bitter taste, nausea, poor appetite, and occasional symptoms, such as diarrhea, vomiting, drug eruption, insomnia, constipation, and lethargy. The adverse events rates of quadruple therapy and triple therapy were 42.3 and 60.0%, respectively.
de Boer et al.[75] (1998) Tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 7 days vs ranitidine bismuth citrate 400 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 7 days vs ranitidine bismuth citrate 400 mg BID, clarithromycin 500 mg BID for 14 days	OL, RCT, PG Patients with upper gastrointestinal symptoms and infected with *H pylori*	N=168 8 weeks	Primary: Endoscopy performed six weeks after completion of treatment to determine *H pylori* infection, defined as a positive CLOtest, confirmed by histology or culture Secondary: Safety	Primary: Logistical regression analysis determined that there was no difference between the 7-day and 14-day treatments. Intent-to-treat analysis cure rate for the ranitidine bismuth citrate, tetracycline, and metronidazole treatment group was 86%. The cure rate for the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group was 92%. The cure rate for the ranitidine bismuth citrate and clarithromycin treatment group was 95%. Per-protocol cure rates were 89%, 93%, and 96% respectively. There was no statistical difference between the three groups. Secondary: Side effects were comparable among the treatment groups. Overall, 32% of patients in the ranitidine bismuth citrate, tetracycline, metronidazole treatment group, 18% of the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group, and 23% of the ranitidine bismuth citrate and clarithromycin treatment group reported side effects during the trial period (P=0.249).
Altintas et al.[76]	RCT	N=52	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2004) Tetracycline 1 g BID, ranitidine-bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 14 days (triple therapy) vs ranitidine-bismuth citrate 1 g BID for 14 days and azithromycin 500 mg QD for 7 days (dual therapy)	Patients ≥18 years of age who were resistant to triple therapy consisting of a PPI, clarithromycin and amoxicillin for the treatment of *H pylori*	6 weeks	Eradication rates of *H pylori* as confirmed by endoscopy and biopsy Secondary: Improvement in symptoms of endoscopic gastritis	There was a significant difference between the treatment groups. Eradication rates for triple and dual therapy were 44.4% and 12%, respectively (P=0.01). Secondary: There were significant improvements in the severity of endoscopic gastritis in both groups (P=0.01), but no significant differences between the two groups (P=0.600).
Luther et al.[77] (2010) Tetracycline, metronidazole, bismuth-containing compound, and proton-pump inhibitor (bismuth quadruple therapy) vs clarithromycin triple therapy (amoxicillin, clarithromycin, and proton-pump inhibitor)	MA Patients with *H. pylori* infection	N=1,679 (9 trials) Variable duration	Primary: Eradication rate, compliance rate, adverse events	Primary: The eradication rate with bismuth quadruple therapy was 78.3% compared to 77% with clarithromycin triple therapy (RR, 1.002, 95% CI, 0.936 to 1.073). The compliance rate with bismuth quadruple therapy was 92.6% compared to 98.9% with clarithromycin triple therapy (RR, 0.99; 95% CI, 0.938 to 1.045). The overall incidence of adverse events in patients receiving bismuth quadruple therapy was 35.5% compared to 35.4% with clarithromycin triple therapy (RR, 1.037; 95% CI, 1.037 to 1.135).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cheon et al.[38] (2006) Tetracycline 500 mg PO QID, pantoprazole 40 mg PO BID, tripotassium dicitrate bismuthate 300 mg PO QID, amoxicillin-clavulanate 1,000 mg PO BID (PBAT) vs tetracycline 500 mg PO QID, pantoprazole 40 mg PO BID, tripotassium dicitrate bismuthate 300 mg PO QID, and metronidazole 500 mg PO TID (PBMT)	RCT Patients infected with *H pylori*	N=54 7 days	Primary: Efficacy (evaluated by histology, rapid urease test and ^{13}C-urea breath test) Secondary: Tolerability	Primary: The *H pylori* eradication rates were 16.0% and 17.4% with PBAT and 65.5% and 70.4% with PBMT by intention-to-treat (*P*<0.001) and per-protocol analyses (P<0.001), respectively. In patients who received PBAT, the eradication rates were only 16.7% (2/12) for both amoxicillin and tetracycline-susceptible *H pylori* strains. Secondary: There was no significant difference in adverse events between the treatment (P=0.343).
Chi et al.[39] (2003) Tetracycline, amoxicillin, omeprazole and bismuth salts vs	RCT Patients who failed 1-week triple therapy of *H pylori*	N=100 6 weeks	Primary: Eradication rates	Primary: The *H pylori* eradication rates by intention-to-treat and per protocol analysis were higher in the tetracycline group than in the metronidazole group (intention-to-treat: 78% vs 58%, P<0.05; per protocol: 89% vs 67%, P<0.05). In the metronidazole group, but not in the tetracycline group, the per protocol eradication rate of quadruple therapy was lower for the infected isolates with metronidazole resistance than for those without metronidazole resistance (77% vs 33%, P<0.05).

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metronidazole plus amoxicillin, omeprazole and bismuth salts				
Georgopoulos et al.[40] (2002) Tetracycline 500 mg QID, omeprazole 20 mg BID, bismuth 120 mg QID, metronidazole 500 mg BID all PO for 7 days vs tetracycline 500 mg QID, omeprazole 20 mg BID, bismuth 120 mg QID, metronidazole 500 mg BID, and clarithromycin 500 mg BID, all PO for 7 days	RCT Patients with persistent *H pylori* infection following omeprazole-clarithromycin-amoxicillin eradication therapy	N=95 6 years	Primary: Eradication rates, sensitivity	Primary: Of the 95 randomized patients, 93% completed the study. Eradication was achieved in 84% and 59% of the tetracycline- and clarithromycin-containing groups, respectively (P=0.007). On multivariate regression analysis, the sensitivity of *H pylori* to metronidazole had a likelihood ratio of 5.2 (P=0.022), followed by the type of quadruple therapy (likelihood ratio, 4.4; P=0.036).
Laine et al.[41] (2003) Tetracycline 125 mg bismuth biskalcitrate 140 mg, and metronidazole 125 mg all PO QID	MC, RCT Patients with active duodenal ulcer or diagnosed within the past 5 years with infection documented by ^{13}C-urea breath test plus	N=320 10 days	Primary: Eradication rates, sensitivity Secondary: Adverse events	Primary: Intent-to-treat eradication rates were 87.7% for OBMT and 83.2% for OAC (P=0.29). OBMT eradicated 91.7% metronidazole-sensitive and 80.4% metronidazole-resistant strains (P=0.06). OAC eradicated 92.1% clarithromycin-sensitive and 21.4% clarithromycin-resistant strains (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
with omeprazole 20 mg PO BID (OBMT) vs omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg, all PO BID (OAC)	histology or culture			Secondary: Adverse events occurred in 58.5% of OBMT patients and 59.0% of OAC patients.
Wong et al.[42] (2006) Tetracycline 500 mg QID, lansoprazole 30 mg BID, metronidazole 400 mg TID, and bismuth subcitrate 120 mg QID all PO for 7 days (quadruple). vs lansoprazole 30 mg, amoxicillin 1 g, levofloxacin 500 mg, PO BID for 7 days (LAL)	RCT Patients who failed *H pylori* eradication (varying regimens)	N=106 7 days	Primary: Eradication rates	Primary: Eradication rates were 57% for the LAL group and 71% for the quadruple group (P=0.140). Metronidazole, clarithromycin, amoxicillin and levofloxacin resistance was found in 76%, 71%, 0% and 18% of patients, respectively. Levofloxacin resistance led to treatment failure in the LAL group. For patients with dual resistance to metronidazole and clarithromycin, the eradication rates were 79% in the LAL group (levofloxacin-sensitive) and 65% in the quadruple group (P=0.34).
Genitourinary Infections				
Mena et al.[12] (2009) Doxycycline 100 mg BID for 7 days	RCT, SC Men with nongonococcal urethritis	N=398 6 weeks	Primary: Persistence or recurrence of *M. genitalium* infection	Primary: From the initial study population enrolled, 36 men in the azithromycin group and 42 men in the doxycycline group tested positive at the initial study enrollment for *M. genitalium*. Of those testing positive at initial follow-up (10-17 days post therapy), 13% (95% CI, 3 to 35) were from the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs azithromycin 1 gram as a single dose				azithromycin group compared to 55% in the doxycycline group (95% CI, 36 to 72; P=0.002). Of the 15 persistently *M. genitalium* infected men who were clinically cured at the early initial follow-up visit, 47% experienced clinical relapse over the subsequent 2-6 weeks.
Heystek et al.[13] (2009) Doxycycline 100 mg BID for 14 days, metronidazole 400 mg TID for 14 days, ciprofloxacin 500 mg as a single dose vs moxifloxacin 400 mg QD for 14 days	RCT, MC, DB Women with uncomplicated pelvic inflammatory disease (PID)	N=434 14 days	Primary: Clinical success 2 to 14 days posttreatment (clinical cure and improvement combined) Secondary: Clinical cure rate at 2 to 14 days posttreatment, clinical success rate at 21 to 35 days posttreatment (clinical failures at day 2 to 14 posttreatment carried forward for follow-up), bacteriological response	Primary: Clinical success rates 2 to 14 days following treatment were 96.6% with moxifloxacin and 98% with the comparator regimen in the PP population (95% CI -4.5 to 1.6) Clinical success rates were 77.0% with moxifloxacin and 76.7% with the comparator regimen in the ITT population (95% CI, -5.8 to 6.9). Moxifloxacin was found to be non-inferior to the comparator arm. Secondary: At 2 to 14 days posttreatment, clinical cure rates were 81.5% with moxifloxacin and 83.2% with the comparator regimen in the PP population (95% CI -9.2 to 5.1). Clinical cure rates were 64.7% with moxifloxacin and 65.0% with the comparator regimen in the ITT population (95% CI, -7.5 to 7.0). Clinical success rates 21 to 35 days following treatment were 93.8% with moxifloxacin and 91.3% with the comparator regimen in the PP population (95% CI -3.8 to 7.4). Clinical success rates were 60.1% with moxifloxacin and 56.8% with the comparator regimen in the ITT (95% CI, -5.8 to 9.1). In the MBV population, overall bacteriological success rates at 2 to 14 days posttreatment were similar in the two treatment groups (moxifloxacin: 92.5%, comparator 88.2%, P=0.52).
Kovacs et al.[48] (1989) Minocycline 100 mg PO BID for day 1 followed by 100 mg/day for days 2	SB, PRO, RCT Patients with *Chlamydia trachomatis* infection of the cervix	N=103 12 weeks	Primary: Efficacy (resolution of signs and symptoms of infections, and eradication of organism)	Primary: Minocycline and doxycycline showed equal effectiveness in the eradication of mycoplasmas in over 80% of the treated patients. Minocycline appeared to have a slight advantage with respect to the resolution of the gynecological symptoms that were associated with the chlamydial infection (83.3% vs 81.2%)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 10 vs doxycycline 100 mg PO BID for day 1 followed by 100 mg/day for days 2-10			Secondary: Adverse events	A 10-day course of either drug resulted in a negative result of a chlamydial culture for all patients at the follow-up assessment, which occurred between 11 days to 12 weeks after therapy. Secondary: A total of 19 patients reported adverse events and 11 of these patients received minocycline therapy while the remaining 8 patients were treated with doxycycline. The adverse events were generally mild, the most frequent event being gastric upset, which was seen in both treatment groups, and giddiness/dizziness in the minocycline treatment group.
Romanowski et al.[49] (1993) Minocycline 100 mg PO nightly for 7 days vs doxycycline 100 mg PO BID for 7 days	RCT, DB Patients with nongonococcal urethritis, mucopurulent cervicitis, or whose sexual partner had either condition or a positive culture for *Chlamydia* treatments	N=253 7 weeks	Primary: Clinical cure (symptoms subsiding or resolving by day 14) Secondary: Adverse effects	Primary: The proportion with urethritis or cervicitis did not differ by treatment group at any follow-up visit (men: doxycycline, 82%; minocycline, 88%; women: doxycycline, 90%; minocycline, 91%; combined: doxycycline, 85%; minocycline, 89%; P>0.08). Unprotected sexual contact did not affect clinical or microbiological cure rates. Secondary: Adverse effects occurred more frequently in the doxycycline group (men: 43% vs 26%; P=0.05; women: 62% vs 35%; P=0.009). Although the proportion with dizziness did not differ by drug administered (P=0.1), dizziness was reported more often by women (11% vs 3%).
Rosenstock et al.[53] (1985) Tetracycline 2 g as a single dose vs tetracycline 500 mg QID for 10 days vs	RCT Women with signs and symptoms compatible with lower urinary tract infections	N=62 29 to 39 days	Primary: Efficacy (disappearance of symptoms and organism on culture and follow-up visits)	Primary: Single-dose tetracycline cured 75% of women with documented urinary tract infections, compared with 94% in the multi-dose tetracycline group and 54% receiving single-dose amoxicillin. Adding patients who were cured of the initial pathogen but acquired a second pathogen during the month of follow-up, the cure rates were 88%, 94%, and 69%, respectively. Two grams of single-dose tetracycline is as effective as other reported regimens regardless of the susceptibility of the initial pathogen and has minimal toxicity.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amoxicillin 3 g as a single dose				
Respiratory Infections				
Mokabberi et al.[14] (2010) Doxycycline 100 mg IV BID vs levofloxacin 500 mg IV QD Patients were allowed to switch from IV to oral therapy at the discretion of the physician.	PRO, DB, RCT Patients ≥18 years of age with pneumonia requiring hospitalization	N=65 2 months	Primary: Response to treatment, failure to treatment and complications, length of stay	Primary: Efficacy of treatment was not significantly different between the treatment groups (P=0.844). There were two failures in the levofloxacin group and one failure in the doxycycline group (P=0.893). Two patients in the levofloxacin group had side effects (mild diarrhea), while no side effects were noted for doxycycline (P=0.375). The mean time to change from IV to oral for levofloxacin group was 2.73 and 2.88 days for doxycycline group (P=0.647). Length of stay was 5.7 days for levofloxacin and 4.0 days for doxycycline (P<0.001).
Ailani et al.[35] (1999) Doxycycline 100 mg IV every 12 hours vs antibiotic(s) (control group)	RCT, PRO Patients with community-acquired pneumonia	N=87 29 months	Primary: Response to treatment, length of hospitalization	Primary: The mean +/-SD interval between starting an antibiotic and the clinical response was 2.21+/-2.61 days in the doxycycline group compared with 3.84+/-6.39 days in the control group (P=0.001). The mean+/-SD length of hospitalization was 4.14+/-3.08 days in the doxycycline group compared with 6.14+/-6.65 days in the control group (P=0.04).
Sobradillo et al.[37] (1992) Doxycycline 100 mg PO BID for 10 days	DB Patients with pneumonia due to Q fever	P=82 40 days	Primary: Efficacy, adverse events	Primary: Fever showed a more rapid reduction in the doxycycline group. Adverse events were observed in 2 patients receiving doxycycline compared to 11 patients receiving erythromycin (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs erythromycin 500 mg PO every 6 hours for 10 days				
Khajotia et al.[36] (1991) Doxycycline 100 mg PO BID vs ofloxacin 200 mg PO BID vs amoxicillin-clavulanate 200 mg IV BID to TID, followed by 625 mg PO BID to QID	PRO Patients with lower respiratory tract infections	N=241 10 days	Primary: Clinical response Secondary: Adverse events	Primary: The clinical response was rated satisfactory (all pretreatment symptoms disappeared) in 28% of the ofloxacin treatment group and in 22% of the doxycycline and amoxicillin-clavulanate treatment groups. The clinical response was rated improved (all except one symptom improved) in 70% of the ofloxacin treatment group and in 65% of the doxycycline and amoxicillin-clavulanate treatment groups. The clinical response was rated unsatisfactory in 2% of the ofloxacin treatment group and in 13% of the doxycycline and amoxicillin-clavulanate treatment groups. The bacteriologic response was rated satisfactory in 59% of the 39 evaluable ofloxacin-treated patients and in 50% of the 30 patients in the other groups. Secondary: Transient adverse events of mild-to-moderate severity were noted in 9 of the 101 patients in the ofloxacin treatment group compared to 7 of the 60 patients in the doxycycline and amoxicillin-clavulanate treatment groups.
Maesen et al.[52] (1989) Doxycycline 100 mg PO BID for 7 days vs minocycline 100	DB, RCT Patients admitted to the hospital because of purulent exacerbations of chronic respiratory disease	N=41 15 days	Primary: Bacteriological and clinical assessment	Primary: Bacteriological and clinical assessment before and immediately after treatment showed no significant differences between the doxycycline and the minocycline groups, nor did further evaluation after seven days follow-up.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg PO BID for 7 days				
Freire et al.[16] (2010) Tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours plus ceftazidime 2 g IV every 8 hours if needed for *P. aeruginosa* vs imipenem-cilastatin 500 mg to 1g IV every 8 hours plus vancomycin 1g every 12 hours for MRSA (IMI/CIL)	DB, RCT, MC Patients ≥18 years of age with hospital-acquired pneumonia	N=945 7 to 14 days	Primary: Clinical response in clinically evaluable (CE) and clinical modified intent to treat (c-mITT) populations at the test-of-cure (TOC) visit, safety	Primary: In the CE population at the TOC visit, 67.9% of patients receiving TGC and 78.2% of patients receiving IMI/CIL were considered cured. In the c-mITT population, 62.7% of patients receiving TGC and 67.6% of patients receiving IMI/CIL were considered cured. TCG was found to be non-inferior to IMI/CIL in the c-mITT population (P=0.001; 95% CI, -11.0 to 1.3), but not in the CE population (P=0.120; 95% CI -17.8 to -3.0). Patients with ventilator-associated pneumonia (VAP) had lower cure rates at the TOC visit than non-VAP patients in both treatment groups. For patients with VAP, the cure rate for TGC was 47.9% in the CE population and 46.5% in the c-mITT population. The cure rate for IMI/CIL was 70.1% in the CE population and 57.8% in the c-mITT population. For patients with non-VAP, the cure rate for TGC was 75.4% in the CE population and 69.3% in the c-mITT population. The cure rate for IMI/CIL was 81.3% in the CE population and 71.2% in the c-mITT population. Treatment-emergent adverse events (TEAEs) were reported by 78% in all patients, with no significant differences between the 2 treatment groups (P=1.000). The most commonly reported TEAEs were diarrhea, nausea, and vomiting. TGC patients had significantly more nausea (15.4%) and vomiting (12.6%) than patients receiving IMI/CIL (P<0.001). Patients receiving IMI/CIL had a significantly greater frequency of diarrhea (15%) than TGC (P<0.05). Reports of 1 or more serious adverse event (SAE) revealed no statistical difference among both therapies (P=0.940), but more IMI/CIL patients (11.6%) reported respiratory system SAEs vs TGC patients (7.1%). Overall mortality did not differ between the TCG (14.1%) and IMI/CIL (12.2%). More deaths occurred in VAP patients treated with TGC than IMI/CIL.
Tanaseanu et al.[59] (2008)	RCT, DB, MC Patients >18 years	N=891 7-14 days	Primary: Clinical response in clinically	Primary: At the TOC assessment in the CE and c-mITT populations, there were no significant differences in the clinical cure rates for tigecycline (TGC) as

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tigecycline 100 mg IV as an initial dose, followed by 50 mg IV twice daily vs levofloxacin 500 mg IV once or twice daily Patients were allowed to switch to oral levofloxacin after 3 days if specific criteria were met.	of age hospitalized with community-acquired pneumonia		evaluable (CE) and clinical modified intent-to-treat (c-mITT) populations at test-of-cure (TOC) Secondary: Health care resource utilization, safety	compared with levofloxacin (LEV). Tigecycline cured 89.7% of patients and levofloxacin cured 86.3% of patients (95% CI, -2.2 to 9.1, P<0.001 for non-inferiority). In the study in which patients were allowed to switch to oral levofloxacin therapy after ≥3 days of IV administration of either study medication, there were no significant differences in the percentage of CE patients who switched to oral therapy (TGC, 89.9 %; LEV, 87.8%) or in the median duration of oral therapy in either group (3.9 days for TGC vs 3.32 for LEV). In the c-mITT population, tigecycline 81% of patients and levofloxacin cured 79.7% of patients (95% CI -4.5 to 7.1, P<0.001 for non-inferiority). Secondary: In the pooled studies, there was no significant difference between the 2 treatment groups in hospital LOS during the primary hospitalization (TGC: 9.8 days; LEV 9.8 days; P=0.883). There was no difference in mean duration of study antibiotic therapy (TGC 9.8 days; LEV 10.0 days; P=0.453). There were no significant differences between the treatment groups in the rate of rehospitalization, admission for ICU care, admission to emergency room care, use of home health care, or nursing home admissions after discharge from the primary hospitalization. More TGC-treated patients than LEV-treated patients reported that adverse events were considered drug related, and nausea and vomiting occurred at a significantly higher rate for TGC vs LEV (P<0.001). Elevated serum ALT/AST levels occurred at significantly higher rates (P<0.01) for LEV patients compared with TGC patients. Discontinuations for adverse events were low (TGC 6.1% and LEV 8.1%).
Tanaseanu et al.[19] (2009)	DB, RCT, MC Patients ≥18 years	N=428 7 to 14 days	Primary: Clinical response in the clinically	Primary: In the CE population, clinical cure rates at the TOC visit were 88.9% for TGC and 85.3% for levofloxacin (P=0.4025). In the c-mITT population,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours (TGC) vs levofloxacin 500 mg IV QD or BID	of age with a community-acquired pneumonia (CAP)		evaluable (CE) population and clinical modified ITT (c-mITT) populations at the test of cure (TOC) visit (10 to 21 posttreatment) Secondary: Microbiologic eradication rates	clinical cure rates were 83.7% for TGC and 81.5% for levofloxacin (P<0.6269). TGC was found to be non-inferior to levofloxacin (P<0.001). Secondary: In the microbiologically evaluable (ME) population, eradication rates at the TOC visit were similar among the treatment groups for common pathogens. The most common isolate was *S. pneumoniae*, with similar eradication for TGC (92%) and levofloxacin (89%). Both therapies eradicated 100% of penicillin-intermediate and penicillin-resistant strains. *M. pneumoniae* was the most commonly identified atypical organism, and was eradicated in 96% of TGC patients and 92% of levofloxacin patients. No obvious differences in eradication rates of other organisms were found, though the number of other isolates was small.
Dartois et al.[56] (2008) Tigecycline 100 mg loading dose, followed by 50mg every 12 hours IV (TGC) vs levofloxacin 500 mg once or twice daily IV (LEV)	RCT, DB, MC Adult hospitalized patients with community-acquired pneumonia	N=387 7-14 days	Primary: Clinical response in clinically evaluable (CE) and clinical modified intent-to-treat (C-mITT) populations at test-of-cure (TOC) Secondary: Safety	Primary: Tigecycline (TGC) cured 89.6% of patients (95% CI 82.9, 94.3) and levofloxacin (LEV) cured 85.8% (95% CI 78.3, 91.5) with an absolute difference of 3.8% (95% CI -5.3, 12.8; P<0.001 for non-inferiority). For those CE patients with a Fine score of<III or III/IV, TGC cured 90.0% and 88.9%, and LEV cured 88.5% and 83.6%, respectively (P<0.001 for non-inferiority). In c-mITT, TGC cured 84.4% of patients (95% CI 78.1, 89.5) and LEV cured 82.1%) of patients (95% CI 75.5, 87.5) with an absolute difference of 2.3% (95% CI 6.1, 10.8, P<0.001 for non-inferiority). In c-mITT patients with a Fine score of<III or III/IV, TGC cured 86.3% and 81.9%, and LEV cured 80.7% and 83.1%, respectively (P<0.001 for non-inferiority). Secondary: Significantly more TGC-treated patients reported treatment-emergent adverse events than with LEV (58.6% vs 45.9%, respectively; P=0.017). Drug-related adverse events were reported more frequently with TGC than with LEV (40.9% vs 25.1%, respectively; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both regimens were generally well tolerated with only a few patients being withdrawn from the study because of any adverse event (1.6% TGC vs 1.1% LEV).
Miscellaneous Infections				
Wormser et al.[33] (2006) Doxycycline PO for 10 days vs doxycycline PO for 10 days with a single IV dose of ceftriaxone vs doxycycline PO for 20 days	RCT, DB Patients with early Lyme disease	N=180 30 months	Primary: Complete response rate (resolution of erythema migrans and symptoms, return to pre-Lyme-disease health) Secondary: Adverse events	Primary: No significant differences in clinical response were found at 20 days (P>0.2). No significant differences in clinical response were found at 30 months (P>0.2). Secondary: The doxycycline-ceftriaxone group had a significantly higher incidence of diarrhea than 10-day and 20-day doxycycline treatment groups (P<0.001). Patient in the doxycycline-ceftriaxone treatment group were more likely to experience an adverse drug event than patient in the 10-day doxycycline (P=0.055) and 20-day doxycycline (P=0.035) treatment groups.
Roushan et al.[61] (2010) Doxycycline 100 mg twice daily for 45 days plus streptomycin 1 g intramuscularly for 2 weeks (streptomycin-doxycycline group) vs doxycycline 100 mg twice daily for	RCT Patients >10 years of age with brucellosis	N=164 Up to 8 weeks	Primary: Therapeutic failure due to lack of efficacy and relapse Secondary: Safety	Primary: Therapeutic failure was seen in two (2.4%) patients from the gentamicin-doxycycline group and in four (4.9%) patients from the streptomycin-doxycycline group (P=0.68). Relapse occurred in two (2.4%) patients from the gentamicin- doxycycline group and in five (6.1%) patients from the streptomycin-doxycycline group (P=0.44). Success occurred in 78 (95.12%) patients in the gentamicin-doxycycline group and in 73 (89%) patients in the streptomycin-doxycycline group (P=0.25). Secondary: The rates of adverse effects were similar in the gentamicin-doxycycline group (28%) and in the streptomycin-doxycycline group (22%; P=0.5).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
8 weeks plus gentamicin 5 mg/kg once daily for 5 days (gentamicin-doxycycline group)				
Keramat et al.[64] (2009) Doxycycline 200 mg PO QD plus rifampin 15 mg/kg QD (DR group) vs ciprofloxacin 15 mg/kg BID plus rifampin 15 mg/kg QD (CR group) vs ciprofloxacin 15 mg/kg BID plus doxycycline 200 mg QD (CD group)	PRO, RCT Patients ≥18 years of age with acute brucellosis	N=178 8 to 12 weeks	Primary: Response and relapse rates	Primary: Response to therapy was observed in 93.7% of patients at the end of treatment for all 3 groups (DR 96.7%, CR 95.2%, CD 87.3%). There were no significant differences among the treatment groups (P=0.09). Therapeutic failure was seen in 12 cases, though no significant differences were noted among the 3 groups (P=0.88). After 6 months, 12 patients relapsed (DR 7.7%, CR 8.3%, CD 17.5%; P=0.35).
Mwengee et al.[47] (2006) Doxycycline 100 mg (adults) and 2.2 mg/kg (children) PO BID for 7 days vs gentamicin 2.5	RCT, OL Adults and children with symptoms of bubonic, septicemic, or pneumonic plague	N=65 2 weeks	Primary: Efficacy (resolution of fever, bubo swelling, and all other plague symptoms)	Primary: Three patients, 2 of whom were treated with gentamicin and 1 of whom was treated with doxycycline, died on the first or second day of treatment, and these deaths were attributed to advanced disease and complications including pneumonia, septicemia, hemorrhage, and renal failure at the start of therapy. All other patients experienced cure or an improved condition after receiving therapy, resulting in favorable response rates of 94% for gentamicin and 97% for doxycycline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg IM BID for 7 days				
Boulanger et al.[46] (2004) Tetracycline vs gentamicin vs streptomycin vs tetracycline and gentamicin	MA Patients with human plague who were reported in New Mexico during 1985-1999	N=50 14 years	Primary: Efficacy (fever days, hospital days, complications, deaths)	Primary: The mean number of fever days after initiation of antimicrobial therapy was 3.5 days in patients treated with streptomycin, 2.6 days in patients treated with gentamicin, 1.9 days in patients treated with tetracycline and gentamicin, and 2.6 days in patients treated with tetracycline; a difference that was not significant (P=0.23). The mean duration of hospitalization was 6.2 days in patients treated with streptomycin, 7.2 days in patients treated with gentamicin, and 6.0 days in patients treated with tetracycline and gentamicin, a difference that was not significant (P=0.57). There were no deaths among the patients in the 4 treatment groups.
Skalsky et al.[63] (2008) Tetracycline combined with any aminoglycoside vs any tetracycline combined with rifampicin or its derivatives vs combination regimens with a	MA Adults or children with uncomplicated and complicated infections caused by *Brucella* species	30 trials 3 to 36 months	Primary: Relapse and overall failure Secondary: Therapeutic failure, all-cause mortality, discontinuation of treatment, adverse events	Primary and Secondary: <u>Tetracycline-streptomycin vs tetracycline-rifampicin</u> Overall failure was significantly higher with tetracycline-rifampicin (RR 2.30, 95% CI: 1.65 to 3.21). Therapeutic failure was higher with tetracycline-rifampicin, but the difference was not significant (RR 1.54; 95% CI: 0.87 to 2.71). Treatment with tetracycline-rifampicin had to be discontinued more often than treatment with tetracycline-streptomycin (RR 1.43; 95% CI: 1.03 to 2.00). Adverse events and discontinuation because of adverse events were similar for the two treatment groups (RR 1.08; 95% CI: 0.84 to 1.39, and RR 1.20; 95% CI: 0.40 to 3.59, respectively). <u>Quinolone vs non-quinolone based regimens</u> Five trials compared quinolone-rifampicin with doxycycline-rifampicin. Overall failure was non-significantly higher in the quinolone group (RR 1.40; 95% CI: 0.77 to 2.52). Both relapse (RR 1.28; 95% CI: 0.64 to 2.53) and therapeutic failure (RR 1.74; 95% CI: 0.59 to 5.19) were more common in the quinolone arm, but this was not significant. The analysis of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
quinolone vs combination regimens without quinolones vs monotherapy vs combination therapy				adverse events favored quinolone-rifampicin (RR 0.37; 95% CI: 0.22 to 0.63). Discontinuation because of adverse events was reported in a single trial, with no significant difference. Two trials compared quinolone-rifampicin with doxycycline-streptomycin. Overall failure was higher in the quinolone arm (RR 2.28; 95% CI: 1.17 to 4.46). Therapeutic failure (RR 1.57; 95% CI: 0.59 to 4.16) occurred more often with quinolones. There was no difference in rates of adverse events or discontinuation because of adverse events. <u>Monotherapy vs combination treatment regimens</u> Seven trials assessed monotherapy. The studies were subcategorized according to the type of monotherapy. When co-trimoxazole was the monotherapy, overall failure was not significantly different (RR 1.27; 95% CI: 0.81 to 1.99), though therapeutic failure was more common (RR 2.49; 95% CI: 1.26 to 4.89). For tetracycline monotherapy, the respective relative risks were 1.01 (95% CI: 0.58 to 1.77) and 0.25 (95% CI: 0.03 to 2.32). Two trials assessed six months of cotrimoxazole monotherapy compared with short-term combination therapy (28 days). When the analysis was limited to trials that compared similar durations of treatment for combination treatment and monotherapy, overall failure was more common with monotherapy (RR 2.56; 95% CI:1.55 to 4.23), while the two trials that compared long monotherapy with short combination therapy found no significant difference.
Towfigh et al.[15] (2010) Tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours for 4 to 14 days (TGC) vs ceftriaxone 2 g IV	RCT, MC, OL Patients ≥18 years of age with community-origin complicated intra-abdominal infections (cIAIs)	N=473 Up to 35 days	Primary: Clinical response in the clinically evaluable (CE) population at the test-of-cure (TOC) visit Secondary: Bacteriological efficacy and safety	Primary: In the CE population, clinical cure was reported in 70% of patients receiving TGC and in 74% of patients in the CTX/MET group (-4.0; 95% CI, -13.1 to 5.1; P=0.009). TCG was found to be non-inferior to CTX/MET. Secondary: Clinical cure rates for the ME population were 66% with TGC and 70% with CTX/MET (-3.4; 95% CI, -14.5 to 7.8; P=0.020. TCG was found to be non-inferior to CTX/MET. In the c-mITT population, clinical cure was reported in 64% of patients receiving TGC and in 71% of patients receiving CTX/MET (-7.0; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
once daily plus metronidazole 1 to 2 g IV daily in divided doses for 4 to 14 days (CTX/MET)				-15.8 to 1.08; P=0.038. TGC was found to be non-inferior to CTX/MET. *Escherichia coli* and *Bacteroides fragilis* were the most commonly isolated bacteria. For the ME population, clinical cure rates for the different pathogens were similar between the two treatment groups. At TOC in the ME population, infections were cured in 68.0% and 67.0% of all monomicrobial and polymicrobial infections, respectively, in the TGC-treated patients, and 71.5% and 68.3% of all monomicrobial and polymicrobial infections, respectively, in the CTX/MET-treated patients. Adverse events were similar with TGC and CTX/MET. There were no significant differences in the incidence of patients reporting one or more SAEs among the treatment groups (P=1.000). The most frequently reported SAEs overall were abscess (6.6%), infection (1.5%), respiratory failure (1.5%), abdominal pain (1.3%) and ileus (1.3%).
Babinchak et al.[50] (2005) Tigecycline 100 mg as an initial dose, followed by 50 mg IV every 12 hours vs imipenem-cilastatin 500 mg IV every 6 hours	MA Adults with complicated intra-abdominal infections	N=1,642 (2 trials) 47 to 56 days	Primary: Clinical response (infection and associated signs and symptoms resolved) Secondary: Safety	Primary: Clinical cure rates were 86.1% for patients in the tigecycline group, vs 86.2% for patients in the imipenem-cilastatin group (P<0.0001 for non-inferiority). Secondary: Nausea (24.4% tigecycline, 19.0% imipenem-cilastatin [*P*=0.01]), vomiting (19.2% tigecycline, 14.3% imipenem-cilastatin [*P*=0.008]), and diarrhea (13.8% tigecycline, 13.2% imipenem-cilastatin [*P*=0.719]) were the most frequently reported adverse events.
Fomin et al.[58] (2008) Tigecycline 100 mg as an initial dose, followed by 50 mg IV every 12 hours vs	RCT, DB (pooled analysis) Adults with complicated intra-abdominal infections	N=1259 5-14 days	Primary: Clinical response at the test-of-cure visit in the microbiologically evaluable (ME) and microbiological modified intent-to-	Primary: Clinical cure rates at the test-of-cure visit were 92.4% for tigecycline vs 88.8% for imipenem/cilastatin in the ME population (95% CI, 2.2, 9.4). Clinical cure rates for the m-mITT populations were 87.3% for tigecycline vs 83.5% for imipenem/cilastatin (95% CI -2.5, 10.0) at the test-of-cure visit. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
imipenem-cilastatin 500 mg IV every 6 hours			treat (m-mITT) populations Secondary: Safety	The most commonly reported treatment emergent adverse events for tigecycline and imipenem/cilastatin were nausea (14.7% and 11.8%, respectively, P=0.267) and vomiting (10.7% and 7.3%, respectively P=0.146). The imipenem/cilastatin group had significantly higher treatment emergent adverse events of fever, hyperglycemia, and dyspnea (P=0.017, P=0.031, and P=0.011, respectively) compared to tigecycline. The tigecycline treatment group had significantly higher treatment emergent adverse events of amylase and BUN increase (P=0.011 and P=0.003, respectively).
Mallick et al.[60] (2007) Tigecycline 100 mg as an initial dose, followed by 50 mg IV every 12 hours vs imipenem-cilastatin 500 mg IV every 6 hours	RCT, DB (pooled analysis) Adults with complicated intra-abdominal infections	N=1005 5-14 days	Primary: Clinical response, safety, and health care resource utilization	Primary: Clinical cure rates were 88.1% for tigecycline and 87.0% for imipenem–cilastatin (P=0.59). Treatment-emergent adverse events, regardless of study drug causality or severity, occurred in 73.8% of tigecycline- and 71.6% of imipenem–cilastatin-treated patients (P=0.346). Of the three most frequently reported adverse events, tigecycline was associated with a significantly higher rate of nausea (24.4%) relative to imipenem–cilastatin (19.0%; P<0.010) and a significantly higher rate of vomiting (19.2% relative to imipenem–cilastatin (14.3%; P<0.008). There were no significant differences between the groups in terms of occurrence of diarrhea (13.8% with tigecycline; 13.2% with imipenem–cilastatin; P=0.719). There were no significant differences between the tigecycline and the imipenem– cilastatin groups for any health resource utilization, clinical outcome, or antibiotic discontinuation rates.
Chen et al.[18] (2010) Tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours (TGC)	OL, RCT, MC Patients ≥18 years of age with complicated intra-abdominal infection	N=191 ≤2 weeks	Primary: Clinical response at the test-of-cure (TOC) visit (12-37 days after therapy) for the microbiologically evaluable and	Primary: In the microbiologically evaluable population, 86.5% of patients receiving TGC and 97.9% of patients receiving IMI/CIL were cured at the TOC visit (95% CI, -23.05 to 0.7). In the m-ITT population, 81.7% of patients receiving TGC and 90.9% of patients receiving IMI/CIL were cured at the TOC visit (95% CI, -23.4 to 4.9).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs imipenem-cilastatin 500-500 mg every 6 hours (IMI/CIL)			microbiologic modified-ITT (m-ITT) populations	In the clinically evaluable population, 87.0% of patients receiving TGC and 95.4% of patients receiving IMI/CIL were cured at the TOC visit (95% CI, -18.3 to 1.5). In the clinical m-ITT population (those with complicated appendicitis), 80.4% of patients receiving TGC and 89.8% of patients receiving IMI/CIL were cured at the TOC visit (95% CI, -20.3 to 1.6). The overall incidence of treatment-emergent adverse events was 80.4% for TGC compared to 53.9% for IMI/CIL (P<0.001). Adverse events were primarily gastrointestinal in nature, especially nausea (21.6% vs 3.9%; P<0.001) and vomiting (12.4% vs 2.0%; P=0.005).

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily, IV=intravenously, PO=by mouth
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PRO=prospective, R=randomized, RCT=randomized controlled trial, SB=single-blind

Additional Evidence

Dose Simplification
Dunbar-Jacob et al. evaluated compliance with oral therapies for the treatment of pelvic inflammatory disease.[54] Patients were randomly assigned to receive either inpatient therapy (parenteral cefoxitin and doxycycline for 2 days, followed by doxycycline orally for 14 days) or outpatient therapy (parenteral cefoxitin as a single dose and doxycycline orally for 14 days). Patients took an average of 70% of the prescribed doses. The doses of doxycycline were taken for less than half of outpatient days of treatment, unscheduled drug holidays occurred on almost 25% of outpatient days, and only 16.9% of doses were taken within the optimal timing interval. Lee et al. evaluated compliance rates with bismuth subsalicylate, metronidazole, and tetracycline for the treatment of *H. pylori* infections.[55] The enhanced group received medication counseling from a pharmacist, along with a medication calendar and a medication box. There was no significant difference between the groups in the number of patients taking more than 60% of the medications. However, there was a significant difference in the number of patients taking more than 90% of the medications (67% of the control group vs 89% of the enhanced compliance group; P<0.01).

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Tetracyclines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Demeclocycline	tablet	N/A	N/A	$$$$$
Doxycycline	capsule, delayed-release tablet, injection, suspension, syrup, tablet	Adoxa®*, Adoxa Pak®*, Doryx®*, Morgidox®*, Vibramycin®*	$$$-$$$$$	$-$$$$$
Minocycline	capsule, tablet	Dynacin®*	$$$$-$$$$$	$-$$$$$
Oxytetracycline	injection	Terramycin®, Terramycin IM®	$	N/A
Tetracycline	capsule	N/A	N/A	$
Tigecycline	injection	Tygacil®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=not available

X. Conclusions

The tetracyclines are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as numerous miscellaneous infections.[1-8] Demeclocycline, doxycycline, minocycline and tetracycline are available in a generic formulation.

There are many guidelines that define the appropriate place in therapy for the tetracyclines. The specific agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the tetracycline. The tetracyclines are recommended for the treatment of susceptible pathogens causing endocarditis, encephalitis, cholera, *Helicobacter pylori* infections, sexually transmitted diseases, anthrax, infectious exacerbations of COPD, community-acquired pneumonia, intra-abdominal infections, Lyme disease, plague, and tickborne rickettsial diseases.[21-22,26-34,78-81,84]

There are few published studies that directly compare the tetracyclines. Doxycycline and minocycline have demonstrated similar efficacy and safety when used for the treatment of genitourinary and respiratory infections.[48-49,52] The tetracyclines have also been shown to be comparable in efficacy to antibacterial agents in other classes.[14,16,18-19,36,41-42,46-47,51,58,64]

There is insufficient evidence to support that one brand tetracycline is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand tetracyclines within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand tetracycline is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2011. Available from Wolters Kluwer Health, Inc. Accessed September 2011.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2011; September 2011.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed September 2011.
4. Adoxa® [package insert]. Melville, NY: PharmaDerm; March 2008.
5. Doryx® [package insert]. Rockaway, NJ: Warner Chilcott; September 2011.
6. Vibramycin® [package insert]. New York N:, Pfizer Labs; April 2011.
7. Dynacin® [package insert]. Scottsdale, AZ: Medicis; August 2005.
8. Tygacil® [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; January 2011.
9. Mandell GL, Bennett JE, Dolin R. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 6th ed. Philadelphia, PA, Elsevier ; 2005.
10. Klein NC, Cunha BA. New uses of older antibiotics. Med Clin North Am. 2001 Jan;85(1):125-32.
11. May DB. Tetracyclines. In: UpToDate, Hooper, DC (Ed), UpToDate, Waltham, MA, 2011.
12. Mena LA, Mroczkowski TF, Nsuami M, et al. A randomized comparison of azithromycin and doxycycline for the treatment of Mycoplasma genitalium-positive urethritis in men. Clin Infect Dis 2009;48:1649-54.
13. Heystek M, Ross JD, PID Study Group. A randomized double-blind comparison of moxifloxacin and doxycycline/metronidazole/ciprofloxacin in the treatment of acute, uncomplicated pelvic inflammatory disease. Int J STD AIDS 2009;20:690-5.
14. Mokabberi R, Haftbaradaran A, Ravakhah K. Doxycycline vs levofloxacin in the treatment of community-acquired pneumonia. J Clin Pharm Ther 2010;35:195-200.
15. Towfigh S, Pasternak J, Poirier A, et al. A multicentre, open-label, randomized comparative study of tigecycline versus ceftriaxone sodium plus metronidazole for the treatment of hospitalized subjects with complicated intra-abdominal infections. Clin Microbiol Infect 2010;16:1274-81.
16. Freire AT, Melnyk V, Kim MJ, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. Diagn Microbiol Infect Dis 2010;68:140-51.
17. Chuang YC, Chang CM, Aradhya S, et al. Efficacy and safety of tigecycline monotherapy compared with vancomycin-aztreonam in the treatment of complicated skin and skin structure infections in patients from India and Taiwan. J Microbiol Immunol Infect 2011;44:116-24.
18. Chen Z, Wu J, Zhang Y, et al. Efficacy and safety of tigecycline monotherapy vs imipenem/cilastatin in Chinese patients with complicated intra-abdominal infections: a randomized controlled trial. BMC Infect Dis 2010;10:217.
19. Tanaseanu C, Milutinovic S, Calistru PI, et al. Efficacy and safety of tigecycline versus levofloxacin for community-acquired pneumonia. BMC Pulm Med 2009;9:44.
20. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005 Nov 15;41(10):1373-406.
21. Chey W, Wong B. American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection. Am J Gastroenterol 2007; 102:1808-1825.
22. Hunt R, Fallone C, Veldhuyzan van Zanten S, Sherman P, et al., CHSG 2004 participants. Canadian Helicobacter Study Group Consensus Conference: Update on the management of Helicobacter pylori--an evidence-based evaluation of six topics relevant to clinical outcomes in patients evaluated for H pylori infection. Can J Gastroenterol. 2004; 18(9):547-554.
23. Malfertheiner P, Megraud F, O'Morain C., et al. Current Concepts in the Management of Helicobacter pylori Infection. The Maastricht 2-2000 Consensus Report. European Helicobacter Pylori Study Group. Aliment Pharmacol Ther 2002; 16:167-180.
24. Veldhuyzen van Zanten SJ, Flook N, Chiba N, Armstrong D, An evidence-based approach to the management of uninvestigated dyspepsia in the era of Helicobacter pylori. Canadian Dyspepsia Working Group. CMAJ. 2000; 162(suppl 12):S3-23.
25. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52:1-38.
26. Chapman AS, Bakken JS, Folk SM, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States. MMWR 2006;55(RR-4):1-27.

27. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1-110.
28. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2010. 117 p. Available at: www.goldcopd.com. Accessed October 2011.
29. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-72.
30. Ramsdell J, Narsavage GL, Fink JB; American College of Chest Physicians' Home Care Network Working Group. Management of community-acquired pneumonia in the home: an American College of Chest Physicians clinical position statement. Chest. 2005 May;127(5):1752-63.
31. Inglesby TV, Dennis DT, et al. Plague as a Biological Weapon: Medical and Public Health Management. 2000 May;283(17): 2281-90.
32. Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, et al; Working Group on Civilian Biodefense. Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA 2002;287(17):2236-52.
33. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis. Clin Infect Dis. 2006;43:1089–134.
34. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50:133-64.
35. Ailani RK, Agastya G, et al. Doxycycline is a cost-effective therapy for hospitalized patients with community-acquired pneumonia. Arch Int Med. 1999 Feb;159(3):266-70.
36. Khajotia RR, Vetter N, Harazin H. Ofloxacin in the treatment of lower respiratory tract infections: report of a prospective, comparative trial. Clin Ther. 1991 Jul-Aug;13(4):460-6.
37. Sobradillo V. Zalacain, R. Antibiotic treatment in pneumonia due to Q fever. Thorax. 1992 Apr;47(4):276-278.
38. Cheon JH. Kim, SG. Combinations containing amoxicillin-clavulanate and tetracycline are inappropriate for Helicobacter pylori eradication despite high in vitro susceptibility. J Gastroenterol Hepatol. 2006 Oct;21(10):1590-5.
39. Chi CH, Lin CY. Quadruple therapy containing amoxicillin and tetracycline is an effective regimen to rescue failed triple therapy by overcoming the antimicrobial resistance of Helicobacter pylori. Aliment Pharmacol Ther. 2003 Aug;18(3):347-53.
40. Georgopoulos SD, Ladas SD, et al. Effectiveness of two quadruple, tetracycline- or clarithromycin-containing, second-line, Helicobacter pylori eradication therapies. Aliment Pharmacol Ther. 2002 Mar;16(3):569-75.
41. Laine L, Hunt R, et al. Bismuth-based quadruple therapy using a single capsule of bismuth biskalcitrate, metronidazole, and tetracycline given with omeprazole versus omeprazole, amoxicillin, and clarithromycin for eradication of Helicobacter pylori in duodenal ulcer patients: a prospective, randomized, multicenter, North American trial. Am J Gastroenterol. 2003 Mar;98(3):562-7.
42. Wong WM, Gu, QC, et al. Lansoprazole, levofloxacin and amoxicillin triple therapy vs quadruple therapy as second-line treatment of resistant Helicobacter pylori infection. Aliment Pharmacol Ther. 2006 Feb;23(3):421-7.
43. Wormser GP, Ramanathan R, et al. Duration of antibiotic therapy for early Lyme disease. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2003 May 6;138(9):697-704.
44. Cortelli JR, Querido SM. Longitudinal clinical evaluation of adjunct minocycline in the treatment of chronic periodontitis. J Periodontol. 2006 Feb;77(2):161-6.
45. Preshaw PM, Hefti AF. Subantimicrobial dose doxycycline enhances the efficacy of scaling and root planing in chronic periodontitis: a multicenter trial. J Periodontol. 2004 Aug;75(8):1068-76.
46. Boulanger LL, Ettestad P. Gentamicin and tetracyclines for the treatment of human plague: review of 75 cases in New Mexico, 1985-1999. Clin Infect Dis. 2004 Mar;38(5):663-9.
47. Mwengee W. Butler, T. Treatment of plague with gentamicin or doxycycline in a randomized clinical trial in Tanzania. Clin Infect Dis. 2006 Mar;42(5):614-21.
48. Kovacs GT, et al. A prospective single-blind trial of minocycline and doxycycline in the treatment of genital chlamydia trachomatis infection in women. Med J Aust. 1989 May 1;150(9):483-5.
49. Romanowski B, et al. Minocycline compared with doxycycline in the treatment of nongonococcal urethritis and mucopurulent cervicitis. Ann Intern Med. 1993 July:119(1):16-22.

50. Babinchak T, Ellis-Grosse E, et al. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. Clin Infect Dis. 2005 Sep;41 Suppl 5:S354-67.
51. Breedt J, Teras J, et al. Safety and efficacy of tigecycline in treatment of skin and skin structure infections: results of a double-blind phase 3 comparison study with vancomycin-aztreonam. Antimicrob Agents Chemother. 2005 Nov;49(11):4658-66.
52. Maesen FP, Davies BI, vanden Bergh JJ. Doxycycline and minocycline in the treatment of respiratory infections: a double-blind, comparative clinical, microbiological and pharmacokinetic study. J Antimicrob Chemother. 1989 Jan;23(1):123-9.
53. Rosenstock J, Smith LP, et al. Comparison of single-dose tetracycline hydrochloride to conventional therapy of urinary tract infections. Antimicrob Agents Chemother. 1985 Apr;27(4):652-4.
54. Dunbar-Jacob J, Sereika SM, foley SM, et al. Adherence to oral therapies in pelvic inflammatory disease. J Womens Health. 2004 Apr;13(3):285-91.
55. Lee M, Kemp JA, Canning A, et al. A randomized controlled trial of an enhanced patient compliance program for Helicobacter pylori therapy. Arch Int Med. 1999 Oct 25;159(19):2312-6.
56. Dartois N, Castaing N, Gandjini H, et al. Tigecycline versus levofloxacin for the treatment of community-acquired pneumonia: European experience. J Chemother 2008;20 (Suppl 1):28-35.
57. Teras J, Gardovskis J, Vaasna T, et al. Overview of tigecycline efficacy and safety in the treatment of complicated skin and skin structure infections - a European perspective. J Chemother 2008;20(Suppl 1):20-7.
58. Fomin P, Koalov S, Cooper A, et al. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections - the European experience. J Chemother 2008;20 (Suppl 1):12-9.
59. Tanaseanu C, Bergallo C, Teglia O, et al. Integrated results of 2 phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia. Diagn Microbiol Infect Dis 2008;61:329-38.
60. Mallick R, Sun S, Schell S. Predictors of efficacy and health resource utilization in treatment of complicated intra-abdominal infections: evidence for pooled clinical studies comparing tigecycline with imipenem-cilastatin. Surg Infect (Larchmt) 2007;8:159-72.
61. Roushan MR, Amiri MJ, Janmohammadi N, et al. Comparison of the efficacy of gentamicin for 5 days plus doxycycline for 8 weeks versus streptomycin for 2 weeks plus doxycycline for 45 days in the treatment of human brucellosis: a randomized clinical trial. J Antimicrob Chemother 2010;65:1028-35.
62. Cenizal M, Skiest D, Luber S, et al. Prospective randomized trial of empiric therapy with trimethoprim-sulfamethoxazole or doxycycline for outpatient skin and soft tissue infections in an area of high prevalence of methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother 2007;51:2628-30.
63. Skalsky K, Yahav D, Bishara J, et al. Treatment of human brucellosis: systematic review and meta-analysis of randomised controlled trials. BMJ 2008;336:701-4.
64. Keramat F, Ranjbar M, Mamani M, et al. A comparative trial of three therapeutic regimens: ciprofloxacin-rifampin, ciprofloxacin-doxycycline and doxycycline-rifampin in the treatment of brucellosis. Trop Doct 2009;39:207-10.
65. Kearney DJ, Brousal A. Treatment of *Helicobacter pylori* infection in clinical practice in the United States. Dig Dis Sci. 2000;45(2):2765-71.
66. Magaret N, Burm M, Faigel D, Kelly C, Peterson W, Fennerty MB. A randomized trial of lansoprazole, amoxicillin, and clarithromycin versus lansoprazole, bismuth, metronidazole and tetracycline in the retreatment of patients failing initial *Helicobacter pylori* therapy. Dig Dis. 2001;19:174-8.
67. Miehlk S, Kirsch C, Schneider-Brachert W, Haferland C, Neumeyer M, Bästein E, et al. A prospective, randomized study of quadruple therapy and high dose dual therapy for treatment of *Helicobacter pylori* resistant to both metronidazole and clarithromycin. Helicobacter. 2003;8(4):310-9.
68. Perri F, Festa V, Clemente R, Villani MR, Quitadamo M, Caruso N, et al. Randomized study of two rescue therapies for *Helicobacter pylori*-infected patients after failure of standard triple therapies. Am J Gastroenterol. 2001;96(1):58-62.
69. Katelaris PH, Forbes GM, Talley NJ, Crotty B. A randomized comparison of quadruple and triple therapies for *Helicobacter pylori* eradication: The QUADRATE study. Gastroenterology. 2002;123(6):1763-9.
70. Uygun A, Kadayifci A, Safali M, et al.The efficacy of bismuth containing quadruple therapy as a first-line treatment option for *Helicobacter pylori*. J Dig Dis 2007;8:211-5.
71. Wu DC, Hsu PI, Tseng HH, et al. *Helicobacter pylori* infection: a randomized, controlled study comparing 2 rescue therapies after failure of standard triple therapies. Medicine (Baltimore) 2011;90:180-5.
72. Songür Y, Senol A, Balkarli A, et al. Triple or quadruple tetracycline-based therapies versus standard triple treatment for *Helicobacter pylori* treatment. Am J Med Sci 2009;338:50-3.

73. Malfertheiner P, Bazzoli F, Delchier JC, et al. *Helicobacter pylori* eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. Lancet 2011;377:905-13.
74. Zheng Q, Chen WJ, Lu H, et al. Comparison of the efficacy of triple versus quadruple therapy on the eradication of *Helicobacter pylori* and antibiotic resistance. J Dig Dis 2010;11:313-8.
75. de Boer WA, Haeck PWE, Otten MH, Mulder CJJ. Optimal treatment of *Helicobacter pylori* with ranitidine bismuth citrate (RBC): a randomized comparison between two 7-day triple therapies and a 14-day dual therapy. Am J Gastroenterol. 1998;93(7):1101-7.
76. Altintas E, Ulu O, Sezgin O, Aydin O, Camdeviren H. Comparison of ranitidine bismuth citrate, tetracycline and metronidazole with ranitidine bismuth citrate and azithromycin for the eradication of *Helicobacter pylori* in patients resistant to PPI based triple therapy. Turk J Gastroenterol. 2004;15(2):90-3.
77. Luther J, Higgins PD, Schoenfeld PS, et al. Empiric quadruple vs triple therapy for primary treatment of *Helicobacter pylori* infection: Systematic review and meta-analysis of efficacy and tolerability. Am J Gastroenterol 2010;105:65-73.
78. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Eur Heart J 2009;30:2369-413.
79. Bonow R, Carabello B, Chatterjee K et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e1-142.
80. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. Circulation. Jun 2005;111:e394-e434.
81. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM, Whitley RJ, Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303-27.
82. Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, et al; Infectious Diseases Society of America. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis. 2001;32:331-51.
83. Hill DR, Ericsson CD, Pearson RD, Keystone JS, Freedman DO, Kozarsky PE, et al. The practice of travel medicine: Guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006; 43:1499-1539.
84. World Gastroenterology Organization (WGO). WGO practice guideline: acute diarrhea. Munich, Germany: World Gastroenterology Organization (WGO); 2008 Mar. 28 p. http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/01_acute_diarrhea.pdf. Accessed December 2011.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antibacterials, Miscellaneous
AHFS Class 081228
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I. Overview

The miscellaneous antibacterials are a diverse group of products that are used to treat many different types of infections.[1-17] The FDA-approved indications vary depending on the particular agent and antimicrobial properties. It is important to analyze current treatment guidelines and published studies when making therapeutic decisions about the miscellaneous antibacterial agents.

Bacitracin inhibits bacterial cell well synthesis and prevents the incorporation of amino acids and nucleotides into the cell wall.[18] The lincosamides (clindamycin and lincomycin) bind to the 50S subunit of bacterial ribosomes to inhibit protein synthesis.[1-3] Colistimethate and polymyxin B are surface active agents that penetrate and disrupt the bacterial cell membrane.[1-3] Daptomycin is a cyclic lipopeptide that binds to bacterial membranes and causes a rapid depolarization of membrane potential. The loss of membrane potential leads to inhibition of the synthesis of protein, which results in bacterial cell death.[3] Linezolid acts early in translation by binding to a site on the bacterial 23S ribosomal RNA of the 50S subunit. It prevents the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process.[3] Quinupristin and dalfopristin act synergistically by binding to different sites on the bacterial ribosome to disrupt protein synthesis. Dalfopristin has been shown to inhibit the early phase of protein synthesis while quinupristin inhibits the late phase of protein synthesis.[14] Rifaximin binds to bacterial DNA-dependent RNA polymerase, thereby inhibiting bacterial RNA synthesis.[15] Telavancin inhibits bacterial cell wall synthesis by interfering with the polymerization and cross-linking of peptidoglycan.[16] Vancomycin binds to the bacterial cell wall causing immediate inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane.[1-3]

There are two combination products containing bismuth, metronidazole and tetracycline that are included in this review (Helidac® and Pylera®). Both products are used to eradicate *Helicobacter pylori* in patients with duodenal ulcer disease. Helidac® is supplied in a 14-day blister card which contains each of the three antibacterial components as separate dosage forms. Pylera® contains all three of the antibacterial components in a single capsule. Bismuth, metronidazole and tetracycline are all active as antibacterial agents. The antibacterial action of bismuth salts is not well understood.[5,10] Metronidazole is metabolized through reductive pathways into reactive intermediates that have cytotoxic actions.[5,10]Tetracycline interacts with the 30S subunit of the bacterial ribosome and inhibits protein synthesis.[5,10]

The miscellaneous antibacterials that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Bacitracin, clindamycin, colistimethate, polymyxin B sulfate and vancomycin are available in a generic formulation. This class was last reviewed in August 2009.

Table 1. Antibacterials, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Bacitracin	injection	Baciim®*	bacitracin
Bismuth subsalicylate, metronidazole, and tetracycline	combination package	Helidac®	none
Clindamycin	capsule, injection, solution	Cleocin HCl®*, Cleocin Palmitate®*, Cleocin Phosphate®*, Cleocin Phosphate in D5W®	clindamycin, Cleocin®
Colistimethate	injection	Coly-Mycin M Parenteral®*	colistimethate
Colloidal bismuth subcitrate, metronidazole, and tetracycline	capsule	Pylera®	none

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Daptomycin	injection	Cubicin®	none
Lincomycin	injection	Lincocin®	none
Linezolid	injection, suspension, tablet	Zyvox®	none
Polymyxin B sulfate	injection	N/A	polymyxin B sulfate
Quinupristin and dalfopristin	injection	Synercid®	none
Rifaximin	tablet	Xifaxan®	none
Telavancin	injection	Vibativ®	none
Vancomycin	capsule, injection	Vancocin®	vancomycin

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

The miscellaneous antibacterials have been shown to be active against the strains of microorganisms indicated in Tables 2-3. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the antibacterials, miscellaneous that are noted in Table 5. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Antibacterials, Miscellaneous (Drugs B-L)[1-17]

Organism	Bacitracin	Bismuth/ Metronidazole/ Tetracycline	Clindamycin	Colistimethate	Daptomycin	Lincomycin
Gram-Positive Aerobes						
Enterococcus faecalis					✔	
Helicobacter pylori		✔				
Staphylococcus aureus	✔		✔		✔	✔
Staphylococcus epidermidis			✔			
Streptococcus agalactiae			✔		✔	
Streptococcus dysgalactia					✔	
Streptococcus pneumoniae			✔			✔
Streptococcus pyogenes			✔		✔	
Gram-Negative Aerobes						
Enterobacter species				✔		
Escherichia coli				✔		
Klebsiella species				✔		
Pseudomonas aeruginosa				✔		
Gram-Positive Anaerobes						
Clostridium perfringens			✔			
Peptostreptococcus species			✔			
Gram-Negative Anaerobes						
Bacteroides fragilis			✔			
Fusobacterium necrophorum			✔			
Fusobacterium nucleatum			✔			
Prevotella melaninogenica			✔			

Table 3. Microorganisms Susceptible to the Antibacterials, Miscellaneous (Drugs L-V)[1-17]

Organism	Linezolid	Polymyxin B Sulfate	Quinupristin/ Dalfopristin	Rifaximin	Telavancin	Vancomycin
Gram-Positive Aerobes						
Enterococcus faecalis	✔				✔	
Enterococcus faecium	✔				✔	
Staphylococcus aureus	✔		✔		✔	✔
Staphylococcus epidermidis	✔		✔		✔	
Streptococcus agalactiae	✔		✔		✔	
Streptococcus dysgalactia					✔	
Streptococcus pneumoniae	✔					
Streptococcus pyogenes	✔		✔		✔	
Viridans group streptococci	✔					
Gram-Negative Aerobes						
Enterobacter species		✔				
Escherichia coli		✔		✔		
Haemophilus influenzae		✔				
Klebsiella species		✔				
Pseudomonas aeruginosa		✔				
Gram-Positive Anaerobes						
Clostridium difficile						✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous antibacterials are summarized in Table 4.

Table 4. Treatment Guidelines Using the Antibacterials, Miscellaneous

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Guidelines on the Prevention, Diagnosis, and Treatment of Infective Endocarditis[142] (2009)**	• Antibiotic treatment of infective endocarditis due to oral streptococci and group D streptococci: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin or ceftriaxone for 4 weeks ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for 2 weeks ▪ Vancomycin for 4 weeks (in beta-lactam allergic patients) o Penicillin-resistant strains: ▪ Penicillin G or amoxicillin for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks plus gentamicin for 2 weeks (in beta-lactam allergic patients) • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for 4 to 6 weeks plus gentamicin for 3 to 5 days ▪ Vancomycin for 4 to 6 weeks plus gentamicin for 3 to 5 days (penicillin-allergic patients or methicillin-resistant staphylococci) o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks ▪ Vancomycin for at least 6 weeks, rifampin for at least 6 weeks, and gentamicin for 2 weeks (penicillin-allergic patients or methicillin-resistant staphylococci) • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains ▪ Amoxicillin plus gentamicin for 4 to 6 weeks ▪ Ampicillin plus gentamicin for 4 to 6 weeks ▪ Vancomycin plus gentamicin for 6 weeks • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months ▪ Doxycycline plus quinolone for >18 months o *Bartonella* species: ▪ Ceftriaxone or ampicillin IV ▪ Doxycycline orally for 6 weeks plus gentamicin or netilmicin for 3 weeks o *Legionella* species: ▪ Erythromycin IV for 2 weeks, then orally for 4 weeks plus rifampin or ciprofloxacin orally for 6

Clinical Guideline	Recommendation(s)
	weeks o *Mycoplasma* species: ▪ Newer fluoroquinolones for >6 months o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Penicillin G or streptomycin IV for 2 weeks, then cotrimoxazole orally for 1 year ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis (before or without pathogen identification): o Native valves: ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks o Prosthetic valves (early, <12 months post surgery) ▪ Vancomycin IV for 6 weeks, gentamicin IV for 2 weeks, and rifampin orally for 2 weeks o Prosthetic valves (late, ≥12 months post surgery) ▪ Ampicillin-sulbactam IV or amoxicillin-clavulanate IV plus gentamicin IV for 4 to 6 weeks ▪ Vancomycin IV, gentamicin IV, and ciprofloxacin orally for 4 to 6 weeks
American College of Cardiology (ACC)/American Heart Association (AHA): **2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease[137] (2008)**	Endocarditis Prophylaxis • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with CHD o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30-60 minutes before procedure): o Oral: amoxicillin o Unable to take oral medications: Ampicillin, cefazolin or ceftriaxone o Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis* o Penicillin G or ceftriaxone for 4 weeks o Ceftriaxone plus gentamicin for 2 weeks o Vancomycin for 4 weeks in patients allergic to penicillin • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin

Clinical Guideline	Recommendation(s)
	○ Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2 weeks ○ Vancomycin for 4 weeks in patients allergic to penicillin • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin ○ Ampicillin for 4 to 6 weeks or penicillin G plus gentamicin for 4 to 6 weeks ○ Vancomycin plus gentamicin for 6 weeks in patients allergic to penicillin • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials ○ Oxacillin-susceptible strains ▪ Nafcillin or oxacillin for 6 weeks plus the optional addition of gentamicin for 3 to 5 days ▪ Cefazolin for 6 weeks with the optional addition of gentamicin in patients allergic to penicillin ○ Oxacillin-resistant strains ▪ Vancomycin for 6 weeks ○ Oxacillin-resistant strains • Therapy for prosthetic valve endocarditis caused by staphylococci ○ Oxacillin-susceptible strains ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks ○ Oxacillin-resistant strains ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks • Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms ○ Ceftriaxone for 4 weeks ○ Ampicillin-sulbactam for 4 weeks ○ Ciprofloxacin for 4 weeks • Therapy for culture-negative endocarditis including *Bartonella* endocarditis ○ Native valve ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for 4 to 6 weeks ○ Prosthetic valve (early; ≤1 year) ▪ Vancomycin for 6 weeks, plus gentamicin for 2 weeks, plus cefepime for 6 weeks, plus rifampin for 6 weeks ○ Prosthetic valve (late; >1 year) ▪ Suspected *Bartonella*, culture negative • Ceftriaxone for 6 weeks plus gentamicin with/without doxycycline for 6 weeks ▪ Documented *Bartonella*, culture positive • Doxycycline for 6 weeks plus gentamicin for 2 weeks
American Heart Association (AHA): **Infective Endocarditis: Diagnosis, Antimicrobial Therapy, and Management of Complications**[28] **(2005)**	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus bovis*: ○ Penicillin-susceptible strains ▪ Penicillin G or ceftriaxone for 4 weeks ▪ Penicillin G or ceftriaxone plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy)

Clinical Guideline	Recommendation(s)
	o Penicillin-resistant strains: ▪ Penicillin G or ceftriaxone for 4 weeks plus gentamicin for 2 weeks ▪ Vancomycin for 4 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus bovis*: o Penicillin-susceptible strains ▪ Penicillin G or ceftriaxone for 6 weeks with or without gentamicin for 2 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Penicillin-resistant strains: ▪ Penicillin G or ceftriaxone for 6 weeks plus gentamicin for 6 weeks ▪ Vancomycin for 6 weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for 6 weeks with the option of adding gentamicin for 3-5 days ▪ For penicillin-allergic individuals: cefazolin for 6 weeks with the option of adding gentamicin for 3-5 days o Oxacillin-resistant strains ▪ Vancomycin for 6 weeks • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) o Oxacillin-resistant strains ▪ Vancomycin plus rifampin (for at least 6 weeks) and gentamicin (for 2 weeks) • Therapy for native valve or prosthetic valve enterococcal endocarditis o Strains susceptible to penicillin, gentamicin, and vancomycin: ▪ Ampicillin or penicillin G plus gentamicin for 4-6 weeks ▪ Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Strains susceptible to penicillin, streptomycin, and vancomycin and resistant to gentamicin: ▪ Ampicillin or penicillin G plus streptomycin for 4-6 weeks ▪ Vancomycin plus streptomycin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) o Strains resistant to penicillin and susceptible to aminoglycosides and vancomycin: ▪ β-lactamase–producing strain: • Ampicillin-sulbactam plus gentamicin for 6

Clinical Guideline	Recommendation(s)
	weeks • Vancomycin plus gentamicin for 6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy) ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for 6 weeks o Strains resistant to penicillin, aminoglycosides and vancomycin: ▪ *E. faecium*: linezolid or quinupristin-dalfopristin for at least 8 weeks ▪ *E. faecalis*: imipenem/cilastatin plus ampicillin or ceftriaxone plus ampicillin for at least 8 weeks • Therapy for both native and prosthetic valve endocarditis caused by HACEK microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin-sulbactam or ciprofloxacin for 4-6 weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin, gatifloxacin, or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin for 4-6 weeks ▪ Vancomycin plus gentamicin plus ciprofloxacin for 4-6 weeks (vancomycin therapy recommended only for patients unable to tolerate penicillins) o Prosthetic valve (early, <1 year): ▪ Vancomycin (for 6 weeks) plus gentamicin (for 2 weeks) plus cefepime (for 6 weeks) plus rifampin (for 6 weeks) o Prosthetic valve (late, ≥1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone (for 6 weeks) plus gentamicin (for 2 weeks) with or without doxycycline (for 6 weeks) ▪ Documented *Bartonella*, culture positive: • Doxycycline (for 6 weeks) plus gentamicin for (2 weeks)
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines: Management of Encephalitis[138] (2008)**	<u>Empirical Therapy</u> • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. <u>Bacteria</u> • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or trimethoprim-sulfamethoxazole is recommended • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended;

Clinical Guideline	Recommendation(s)
	trimethoprim-sulfamethoxazole is an alternative in the penicillin-allergic patient • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered • *Tropheryma whipplei:* ceftriaxone, followed by either trimethoprim-sulfamethoxazole or cefixime, is recommended Rickettsioses and Ehrlichioses • *Anaplasma phagocytophilum:* doxycycline is recommended • *Ehrlichia chaffeensis:* doxycycline is recommended • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative Protozoa • *Acanthamoeba:* trimethoprim-sulfamethoxazole plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; trimethoprim-sulfamethoxazole alone and pyrimethamine plus either atovaquone, clarithromycin, azithromycin, or dapsone are alternatives • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended

European Federation of Neurological Societies (EFNS): **Guideline on the Management of Community-acquired Bacterial Meningitis[132] (2008)**	Empirical Therapy
	• Ceftriaxone 2 g every 12–24 hours or cefotaxime 2 g every 6–8 hours.
	• Alternative therapy: Meropenem 2 g every 8 hours or chloramphenicol 1 g every 6 hours.
	• If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg.
	• Ampicillin/Amoxicillin 2 g every 4 hours if *Listeria* is suspected.
	Pathogen Specific Therapy
	• Penicillin-sensitive pneumococcal meningitis:
	  o Benzyl penicillin 250,000 U/kg/day, ampicillin/amoxicillin 2 g every 4 hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every 6–8 hours
	  o Alternative therapy: meropenem 2 g every 8 hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600

Clinical Guideline	Recommendation(s)
	mg every 12 hours, or moxifloxacin 400 mg daily • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin ± rifampicin o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime o Alternative therapy: chloramphenicol–ampicillin/amoxicillin • Listerial meningitis: o Ampicillin or amoxicillin 2 g every 4 hours ± gentamicin 1–2 mg every 8 hours for the first 7– 10 days o Alternative therapy: trimethoprim–sulfamethoxazole 10–20 mg/kg every 6–12 hours or meropenem • *Staphylococcal* species: o Flucloxacillin 2 g every 4 hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem • Pseudomonal meningitis: o Meropenem ± gentamicin
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Bacterial Meningitis[65] (2004)**	Empiric Therapy • Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative CSF Gram stain result: • Age <1 month: ampicillin plus cefotaxime or ampicillin plus an aminoglycoside • Age 1–23 months: vancomycin plus a third-generation cephalosporin • Age 2-50 years: vancomycin plus a third-generation cephalosporin • Age >50 years: Vancomycin plus ampicillin plus a third-generation cephalosporin • Basilar skull fracture: vancomycin plus a third-generation cephalosporin • Penetrating head trauma: Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem • Postneurosurgery: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem • CSF shunt: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem Specific Therapy • Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility. • *Streptococcus pneumoniae* o Penicillin MIC ≥2 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime; alternative therapies include gatifloxacin or moxifloxacin o Cefotaxime or ceftriaxone MIC ≥1.0 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime

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	(consider addition of rifampin if MIC of ceftriaxone is >2 µg/mL); alternative therapies include gatifloxacin or moxifloxacin
	• *Staphylococcus aureus* methicillin susceptible
	  o Standard therapy includes nafcillin or ofloxacin; alternative therapies include vancomycin or meropenem
	• *Staphylococcus aureus* methicillin resistant
	  o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapies include trimethoprim-sulfamethoxazole or linezolid
	• *Staphylococcus epidermidis*
	  o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapy includes linezolid
	• *Enterococcus* species ampicillin resistant
	  o Standard therapy includes vancomycin plus gentamicin
	• *Enterococcus* species ampicillin and vancomycin resistant
	  o Standard therapy includes linezolid

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections[20] (2005)**	Overview
	• Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first- or second-generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of methicillin-resistant S*taphylococcus aureus* (MRSA) strains.
	Animal Bites
	• Oral treatment options
	  o Amoxicillin/clavulanate is recommended.
	  o Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin.
	  o Other options, including fluoroquinolones, trimethoprim-sulfamethoxazole, and cefuroxime, may require an additional agent active against anaerobes, such as metronidazole or clindamycin.
	  o First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *P. multocida* and should be avoided.
	• Intravenous treatment options
	  o β-lactam/β-lactamase combinations, piperacillin/tazobactam, second-generation cephalosporins, and carbapenems.
	  o Second-generation and third-generation cephalosporins may be used but may require the addition of an anti-anaerobic agent.
	Animal Contact
	• Erysipeloid:
	  o For cutaneous infection, penicillin or amoxicillin for 7–10 days seems to be rational.
	  o For patients who are intolerant of penicillins, treatment with cephalosporins, clindamycin, or fluoroquinolones should be effective.
	Cellulitis
	• A large percentage of patients can receive oral medications from the start. Suitable agents include dicloxacillin, cephalexin, clindamycin, or erythromycin, unless streptococci or staphylococci.
	• For parenteral therapy, which is indicated for severely ill patients or for those unable to tolerate oral medications, reasonable choices include a penicillinase-resistant penicillin such as nafcillin, a first-generation

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	cephalosporin such as cefazolin, or, for patients with life-threatening penicillin allergies, clindamycin or vancomycin. • In cases of uncomplicated cellulitis, 5 days of antibiotic treatment is as effective as a 10-day course. <u>Erysipelas</u> • Penicillin, given either parenterally or orally depending on clinical severity, is the treatment of choice. • If staphylococcal infection is suspected, a penicillinase-resistant semisynthetic penicillin or a first-generation cephalosporin should be selected. <u>Human Bites</u> • Clenched-fist injuries often require hospitalization and intravenous antimicrobial therapy with agents such as cefoxitin, ampicillin/sulbactam, ertapenem, or some combination that covers *S. aureus, Haemophilus* species, *E. corrodens,* and β-lactamase–producing anaerobes. • *E. corrodens* is usually resistant to first-generation cephalosporins, macrolides, clindamycin, and aminoglycosides, and these agents should be avoided as monotherapy. • In the type 1 β-lactam–allergic patient, fluoroquinolones plus clindamycin, or trimethoprim-sulfamethoxazole plus metronidazole may be useful. <u>Impetigo</u> • The decision of how to treat impetigo depends on the number of lesions, their location (face, eyelid, or mouth), and the need to limit spread of infection to others. • Patients who have numerous lesions or who are not responding to topical agents should receive oral antimicrobials effective against both *S. aureus* and *S. pyogenes.* • Because *S. aureus* currently accounts for most cases of bullous impetigo, as well as for a substantial portion of nonbullous infections, penicillinase-resistant penicillins or first generation cephalosporins are preferred. • Erythromycin has been a mainstay of pyoderma therapy, but its utility may be lessened in areas where erythromycin-resistant strains of *S. aureus,* or more recently. • Additional therapies include clindamycin or amoxicillin/clavulanate. <u>Necrotizing Infections</u> • Antimicrobial therapy must be directed at the pathogens and used in appropriate doses until repeated operative procedures are no longer needed, the patient has demonstrated obvious clinical improvement, and fever has been absent for 48–72 h. • The best choice of antibiotics for community-acquired mixed infections is a combination of ampicillin-sulbactam plus clindamycin plus ciprofloxacin. The carbapenems, or a combination of cefotaxime plus metronidazole or clindamycin, are also appropriate. In cases of penicillin allergy, alternatives include clindamycin or metronidazole plus an aminoglycoside or fluoroquinolone. • *S aureus* infection, often associated with pyomyositis, should be treated with nafcillin, oxacillin, or cefazolin. Vancomycin should be reserved for resistant strains or can be used in cases of severe penicillin allergy, as well as linezolid, quinupristin-dalfopristin or daptomycin. Clindamycin is limited by its potential of cross-resistance. <u>Surgical Site Infections</u> • If there is minimal surrounding evidence of invasive infection (<5 cm

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	of erythema and induration), and if the patient has minimal systemic signs of infection (a temperature of <38.5°C and a pulse rate of <100 beats/min), antibiotics are unnecessary. • For patients with a temperature of >38.5°C or a pulse rate of >100 beats/min, a short course of antibiotics, usually for a duration of 24–48 h, may be indicated. The antibiotic choice is usually empirical but can be supported by findings of Gram stain and results of culture of the wound contents. • For intestinal or genital tract surgical site infections, single agents such as cefoxitin, ceftizoxime, ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam, or carbapenems are indicated. In cases where facultative and aerobic activity is desired, fluoroquinolones, third-generation cephalosporins, aztreonam, or aminoglycosides are recommended. When anaerobic activity is desired, appropriate treatment includes clindamycin, metronidazole, chloramphenicol or a penicillin agent plus a β-lactamase inhibitor. • In axillary or perineum surgical site infections, cefoxitin, ampicillin-sulbactam or agents indicated for intestinal and genital sites are appropriate.
Infectious Diseases Society of America (IDSA): **Diagnosis and Treatment of Diabetic Foot Infections**[21] **(2004)**	• Empirical antibiotic regimens should be based on the clinical severity of the infection. • Current clinical data does not allow for the recommendation of any specific antibiotic regimen for diabetic foot infections (DFIs). • Suggested agents are derived from available published clinical trials and expert experience. • Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have US Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid is currently specifically approved for diabetic foot infections. • Suggested empirical antibiotic regimens for mild infections: dicloxacillin, clindamycin, cephalexin, trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, levofloxacin • Suggested empirical antibiotic regimens for moderate infections: trimethoprim-sulfamethoxazole, amoxicillin/clavulanate, levofloxacin, cefoxitin, ceftriaxone, ampicillin/sulbactam, linezolid (with or without aztreonam), daptomycin (with or without aztreonam), ertapenem, cefuroxime (with or without metronidazole), ticarcillin/clavulanate, piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin • Suggested empirical antibiotic regimens for severe infections: piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin, imipenem-cilastatin, vancomycin and ceftazidime (with or without metronidazole)
Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults**[133] **(2010)**	Treatment of *Clostridium difficile* infections (CDI) • Discontinue therapy with the inciting antimicrobial agent(s) as soon as possible, as this may influence the risk of CDI recurrence. • When severe or complicated CDI is suspected, initiate empirical treatment as soon as the diagnosis is suspected. • If possible, avoid use of antiperistaltic agents, as they may obscure symptoms and precipitate toxic megacolon. • Metronidazole is the drug of choice for the initial episode of mild-to-moderate CDI. The dosage is 500 mg orally 3 times per day for 10–14

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	days. • Vancomycin is the drug of choice for an initial episode of severe CDI. The dosage is 125 mg orally 4 times per day for 10–14 days. • Vancomycin administered orally with or without intravenously administered metronidazole is the regimen of choice for the treatment of severe, complicated CDI. The vancomycin dosage is 500 mg orally 4 times per day and 500 mg in approximately 100 mL normal saline per rectum every 6 hours as a retention enema, and the metronidazole dosage is 500 mg intravenously every 8 hours. • Treatment of the first recurrence of CDI is usually with the same regimen as for the initial episode but should be stratified by disease severity (mild-to-moderate, severe, or severe complicated), as is recommended for treatment of the initial CDI episode. • Do not use metronidazole beyond the first recurrence of CDI or for long-term chronic therapy because of potential for cumulative neurotoxicity. • Treatment of the second or later recurrence of CDI with vancomycin therapy using a tapered and/or pulse regimen is the preferred next strategy. • No recommendations can be made regarding prevention of recurrent CDI in patients who require continued antimicrobial therapy for the underlying infection.

European Society of Clinical Microbiology and Infectious Diseases (ESCMID): **Treatment Guidance Document for *Clostridium difficile* Infection (CDI)**[134] **(2009)**	Treatment of *Clostridium difficile* infection (CDI)
	• Treatment for an initial episode and a first recurrence of CDI:
	  o If oral therapy is possible: metronidazole 500 mg three times a day for 10 days (non-severe); vancomycin 125 mg four times a day for 10 days (severe).
	  o If oral therapy is impossible: metronidazole 500 mg intravenously three times a day for 10 days (non-severe); metronidazole 500 mg intravenously three times a day for 10 days plus intracolonic vancomycin 500 mg in 100 ml of normal saline every 4 to 12 hours and/or vancomycin 500 mg via nasogastric tube four times a day (severe).
	• Treatment for a second recurrence of CDI and later recurrence:
	  o If oral therapy is possible: vancomycin 125 mg four times a day for 10 days; also consider a taper or pulse strategy.
	  o If oral therapy is impossible: metronidazole 500 mg intravenously three times a day for 10-14 days plus retention enema of vancomycin 500 mg in 100 ml normal saline every 4 to 12 hours and/or vancomycin 500 mg by nasogastric tube four times a day.
	• In all the above-mentioned cases, oral vancomycin may be replaced by teicoplanin 100 mg twice daily.

World Gastroenterology Organization (WGO): **Acute Diarrhea**[135] **(2008)**	General Considerations
	• Antimicrobials are the drugs of choice for empirical treatment of traveler's diarrhea and of community-acquired secretory diarrhea when the pathogen is known.
	• Consider antimicrobial treatment for:
	  o Persistent *Shigella*, *Salmonella*, *Campylobacter*, or parasitic infections
	  o Infections in the aged, immunocompromised patients, and patients with impaired resistance, sepsis, or with prostheses
	  o Moderate/severe traveler's diarrhea or diarrhea with fever and/or with bloody stools (quinolones as initial therapy or

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	co-trimoxazole as a second choice)
	• Nitazoxanide may be appropriate for *Cryptosporidium* and other infections, including some bacteria.
	• Rifaximin may also be useful.
	<u>Antimicrobial Agents for the Treatment of Specific Causes of Diarrhea</u>
	• *Cholera*
	  o First-line: doxycycline or tetracycline
	  o Alternative: azithromycin or ciprofloxacin
	• *Shigellosis*
	  o First-line: ciprofloxacin
	  o Alternative: pivmecillinam or ceftriaxone
	• *Amebiasis*
	  o First-line: metronidazole
	• *Giardiasis*
	  o First-line: metronidazole
	• *Campylobacter*
	  o First-line: azithromycin

Infectious Diseases Society of America (IDSA): **The Practice of Travel Medicine[26] (2006)**	<u>Chemoprophylaxis</u> • Bismuth subsalicylate–containing formulations and antibiotics have been proven effective in preventing traveler's diarrhea. • Probiotics, such as lactobacillus, have not demonstrated sufficient efficacy to be recommended. • Widespread drug resistance renders doxycycline and trimethoprim-sulfamethoxazole (TMP-SMX) no longer useful for prevention of traveler's diarrhea. • Chemoprophylaxis can contribute to development of resistant enteric bacteria and potentially predispose the traveler to infection with other deleterious pathogens, such as *Clostridium difficile.* • The routine use of antibiotic prophylaxis for travelers' diarrhea is not generally recommended. • Chemoprophylaxis may be considered in healthy travelers for whom staying well is critical and in special-needs travelers in whom the risk for diarrhea is increased or the consequences of a diarrheal episode may be severe. • When considering chemoprophylaxis, fluoroquinolone antibiotics remain the first choice. • Chemoprophylaxis should be recommended for no more than 2–3 weeks. <u>Treatment</u> • Fluid replacement and a diet restricted to liquids and bland foods may be appropriate, though they may not provide additional benefits beyond antibiotic treatment. • Symptomatic therapy with bismuth subsalicylate may be recommended in mild cases of diarrhea, but better agents exist for moderate-to-severe disease. • Loperamide has become the antimotility agent of choice. It is more efficacious in controlling diarrhea than bismuth subsalicylate and has an onset of action within the first 4 hours after ingestion. When it is used in combination with an antibiotic, there may be rapid improvement of traveler's diarrhea. • Antibiotics are effective in the treatment of traveler's diarrhea and can reduce the average duration of disease from several days to ~1 day. • Antibiotics that are recommended include fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin, levofloxacin), azithromycin, and rifaximin.

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	• Fluoroquinolones remain predictably active for empiric therapy in most parts of the world and remain the drugs of first choice. • Antibiotics that are no longer recommended because of drug resistance worldwide are the sulfonamides, neomycin, ampicillin, doxycycline, tetracycline, trimethoprim alone, and TMP-SMX.
American College of Gastroenterology: **Guideline on the Management of *Helicobacter pylori* Infection[22] (2007)**	• The recommended primary therapies for *H. pylori* infection include: a PPI, clarithromycin, and amoxicillin, or metronidazole (clarithromycin-based triple therapy) for 14 days or a PPI or H2RA, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10–14 days.
Canadian Helicobacter Study Group Consensus Conference: **Update on the Management of *Helicobacter pylori*[23] (2004)**	• A quadruple combination of a PPI, bismuth, tetracycline, and metronidazole for 10-14 days can be considered first-line therapy for the eradication of *H. pylori.* • Eradication rates with the recommended quadruple therapy are comparable with those achieved with PPI-based triple therapy regimens in patients who adhere to the protocol. Given the lower number of tablets and twice daily dosing, in practice, PPI-based triple therapy may be the first choice.
European *Helicobacter pylori* Study Group: **Current Concepts in the Management of *H. pylori* Infection–The Maastricht 2-2000 Consensus Report[24] (2002)**	• First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole. • Second-line therapy should use quadruple therapy with a PPI, bismuth, metronidazole, and tetracycline. • When bismuth is not available, second-line therapy should be triple therapy with a proton-pump inhibitor.
Canadian Dyspepsia Working Group: **An Evidence-Based Approach to the Management of Uninvestigated Dyspepsia in the Era of *Helicobacter pylori*[25] (2000)**	• First-line eradication therapies for *H. pylori* are triple therapies of a PPI plus amoxicillin plus clarithromycin (PPI + AC), or a PPI plus metronidazole plus clarithromycin (PPI + MC), twice daily for 1 week; or ranitidine bismuth citrate plus either AC or MC. • If the first eradication therapy has failed, the action recommended by the Canadian *Helicobacter pylori* Consensus Conference is to use a different first-line therapy than that used initially (e.g., switch from PPI + AC to PPI + MC). • An alternative therapy is a 14-day quadruple regimen of a PPI (twice daily) plus bismuth (subsalicylate, 2 tablets 4 times daily) plus metronidazole (250 mg 4 times daily) plus tetracycline (500 mg 4 times daily) (PPI + BMT). • For the management of patients negative for *H. pylori*, a PPI is the first-line therapy choice.

Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines[135] (2010)**	<u>Bacterial Vaginosis</u>
	• Recommended regimens:
	  o Metronidazole 500 mg orally twice a day for 7 days
	  o Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days
	  o Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days
	• Alternative regimens:
	  o Tinidazole 2 g orally once daily for 2 days
	  o Tinidazole 1 g orally once daily for 5 days
	  o Clindamycin 300 mg orally twice daily for 7 days
	  o Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days
	<u>Pelvic Inflammatory Disease</u>
	• Recommended parenteral regimen A:
	  o Cefotetan 2 g IV every 12 hours

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	o Cefoxitin 2 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours • Recommended parenteral regimen B: o Clindamycin 900 mg IV every 8 hours plus gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) can be substituted. • Alternative parenteral regimens: o Ampicillin/Sulbactam 3 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours • Recommended oral regimen: o Ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days o Cefoxitin 2 g IM in a single dose and probenecid, 1 g orally administered concurrently in a single dose, plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days o Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
American Academy of Pediatrics (AAP): **Clinical Practice Guideline: Management of Sinusitis[138] (2001)**	• Antibiotics are recommended for the management of acute bacterial sinusitis to achieve a more rapid clinical cure. • The principle bacterial pathogens in bacterial sinusitis are *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis.* • For children younger than 2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in degree of severity, who do not attend day care, and have not recently been treated with an antimicrobial, amoxicillin is recommended. • If the patient is allergic to amoxicillin, either cefdinir, cefuroxime, or cefpodoxime can be used (only if the allergic reaction was not a type 1 hypersensitivity reaction). • In cases of serious allergic reactions, clarithromycin or azithromycin can be used in an effort to select an antimicrobial of an entirely different class. The Food and Drug Administration has not approved azithromycin for use in patients with sinusitis. • Alternative therapy in the penicillin-allergic patient who is known to be infected with a penicillin-resistant *S pneumoniae* is clindamycin. • If patients do not improve while receiving the usual dose of amoxicillin (45 mg/kg/d), have recently been treated with an antimicrobial, have an illness that is moderate or more severe, or attend day care, therapy should be initiated with high-dose amoxicillin-clavulanate (80–90 mg/kg/d of amoxicillin component, with 6.4 mg/kg/d of clavulanate in 2 divided doses). • Alternative therapies include cefdinir, cefuroxime, or cefpodoxime. A single dose of ceftriaxone, given either intravenously or intramuscularly, can be used in children with vomiting that precludes administration of oral antibiotics. Twenty-four hours later, when the child is clinically improved, an oral antibiotic is substituted to complete the therapy. • Recent pneumococcal surveillance studies indicate that resistance to trimethoprim-sulfamethoxazole and erythromycin-sulfisoxazole is substantial. Therefore, when patients fail to improve while receiving

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	amoxicillin, neither trimethoprim-sulfamethoxazole nor erythromycin-sulfisoxazole are appropriate choices for antimicrobial therapy. • For patients who do not improve with a second course of antibiotics or who are acutely ill, there are 2 options. It is appropriate to consult an otolaryngologist for consideration of maxillary sinus aspiration to obtain a sample of sinus secretions for culture and sensitivity so that therapy can be adjusted precisely. Alternatively, the physician may prescribe intravenous cefotaxime or ceftriaxone (either in hospital or at home) and refer to an otolaryngologist only if the patient does not improve on intravenous antibiotics.

Infectious Diseases Society of America (IDSA): **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age**[139] **(2011)**	<u>Outpatient Treatment</u>
	• Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia (CAP), because viral pathogens are responsible for the great majority of clinical disease.
	• Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate CAP suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*.
	• For patients allergic to amoxicillin, the following agents are considered alternative treatment options:
	  o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil)
	  o Levofloxacin (oral therapy)
	  o Linezolid (oral therapy)
	• Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with CAP caused by atypical pathogens.
	<u>Inpatient Treatment</u>
	• Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with CAP when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *S. pneumoniae*.
	• Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema.
	• Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America.
	• Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *M. pneumoniae* and *C. pneumoniae* are significant considerations.
	• Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *S. aureus*.

Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS): **Consensus Guidelines on the Management of Community-**	• Inpatient, ICU treatment
	  o β-lactam plus either azithromycin or a fluoroquinolone
	  o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam plus either ciprofloxacin or

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Acquired Pneumonia in Adults[27] (2007)	levofloxacin OR o Antipneumococcal, antipseudomonal β-lactam plus an aminoglycoside and azithromycin OR o Antipneumococcal, antipseudomonal β-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone. o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.
American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA): **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia[97] (2005)**	• Select an initial empiric therapy based on the absence or presence of risk factors for multidrug-resistant (MDR) pathogens. These risk factors include prolonged duration of hospitalization (5 days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy. • Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins. • In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics. • Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for MDR pathogens and all disease severity – combination antibiotic therapy is recommended as follows: o Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if MRSA risk factors are present or there is a high incidence locally.
National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Diseases Society of America (HIVMA/IDSA): **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents[140] (2008)**	Treatment of *Toxoplasma* Encephalitis (TE) • The initial therapy of choice for TE consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin. • The preferred alternative regimen for patients with TE who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin. • TMP-SMX was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with TMP-SMX, treatment with this drug may be considered an option. • Acute therapy for TE should be continued for at least 6 weeks, if there is clinical and radiologic improvement.
Infectious Diseases Society of America (IDSA): **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children[30] (2010)**	Community-Acquired Infection in Adults: Mild to Moderate Severity • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with

Clinical Guideline	Recommendation(s)
	substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*E. Coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. <u>Community-Acquired Infection in Adults: High Severity</u> • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *E. coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E. coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended. • Use of agents effective against MRSA or yeast is not recommended in the absence of evidence of infection due to such organisms. <u>Community-Acquired Infection in Pediatric Patients:</u> • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected MRSA or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. <u>Health Care-Associated Infection:</u>

Clinical Guideline	Recommendation(s)
	• Therapy should be based on microbiologic results. To achieve empiric coverage, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. Cholecystitis and Cholangitis: • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.
Infectious Diseases Society of America (IDSA): **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus*[136] (2011)**	Skin and Soft-Tissue Infections (SSTIs) • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired (CA) MRSA is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for CA-MRSA is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of CA-MRSA in outpatients with SSTI, oral antibiotic options include the following: clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and CA-MRSA is desired, options include the following: clindamycin alone or TMP-SMX or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of SSTIs is not recommended. • For hospitalized patients with complicated SSTIs, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for MRSA should be considered pending culture data. Options include the following: vancomycin intravenous (IV), linezolid oral (PO) or IV, daptomycin IV, telavancin IV, and clindamycin IV or PO. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to MRSA-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used.

Clinical Guideline	Recommendation(s)
	• Tetracyclines should not be used in children <8 years of age. • In hospitalized children with cSSTIs, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin IV is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative. MRSA Bacteremia and Infective Endocarditis (Native Valve) • For adults with uncomplicated bacteremia, vancomycin or daptomycin IV for at least 2 weeks is recommended. For complicated bacteremia, 4–6 weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, IV vancomycin or daptomycin for 6 weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. MRSA Bacteremia and Infective Endocarditis (Prosthetic Valve) • IV vancomycin plus rifampin PO/IV for at least 6 weeks plus gentamicin IV for 2 weeks. • In children, vancomycin IV is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from 2 to 6 weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin IV may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. Management of MRSA Pneumonia • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for MRSA is recommended pending sputum and/or blood culture results. • For health care–associated MRSA (HA-MRSA) or CA-MRSA pneumonia, IV vancomycin or linezolid PO/IV or clindamycin PO/IV, if the strain is susceptible, is recommended for 7–21 days, depending on the extent of infection. • In children, IV vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin IV can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid PO/IV is an alternative. Management of MRSA Bone and Joint Infections • Antibiotics available for parenteral administration include IV vancomycin and daptomycin. • Some antibiotic options with parenteral and oral routes of administration include the following: TMP-SMX in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia. • A minimum 8-week course is recommended. Some experts suggest an additional 1–3 months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination

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	therapy with TMP-SMX, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities.
	• For septic arthritis, refer to antibiotic choices for osteomyelitis. A 3 to 4-week course of therapy is suggested.
	<u>Management of MRSA Infections of the CNS</u>
	• Meningitis
	  o IV vancomycin for 2 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid or TMP-SMX.
	  o For CNS shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid (CSF) cultures are repeatedly negative.
	• Brain abscess, subdural empyema, spinal epidural abscess
	  o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and TMP-SMX.
	• Septic thrombosis of cavernous or dural venous sinus
	  o IV vancomycin for 4–6 weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and TMP-SMX.
	  o IV vancomycin is recommended in children.

Infectious Diseases Society of America (IDSA): **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer**[143] **(2010)**	<u>Initial Antibiotic Therapy</u>
	• Oral route:
	  o For low-risk adults only; use ciprofloxacin plus amoxicillin-clavulanate
	• Monotherapy with vancomycin not indicated:
	  o Choose therapy with 1 of the following agents: cefepime or ceftazidime, or imipenem or meropenem
	• Two drugs without vancomycin:
	  o Choose an aminoglycoside plus antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem
	• Vancomycin plus 1 or 2 antibiotics:
	  o Choose cefepime or ceftazidime plus vancomycin, with or without an aminoglycoside; carbapenem plus vancomycin, with or without an aminoglycoside; or antipseudomonal penicillin plus an aminoglycoside and vancomycin
	<u>Modification of Therapy During the First Week of Treatment</u>
	• Patient becomes afebrile in 3–5 days:
	  o Adjust therapy to the most appropriate drug(s). If no etiologic agent is identified and if the patient is at low risk initially, and oral antibiotic treatment was begun with no subsequent complications, continue use of the same drugs.
	  o If the patient was at low risk initially and therapy with intravenous drugs was begun with no subsequent complications, the regimen may be changed after 48 h to oral ciprofloxacin plus amoxicillin-clavulanate for adults or cefixime for children.
	  o If the patient is at high risk initially with no subsequent complications, continue use of the same intravenous drugs.
	• Persistent fever throughout the first 3–5 days:
	  o Reassess therapy on day 3. If there is no clinical worsening, continue use of the same antibiotics; stop vancomycin use if cultures do not yield organisms.
	  o If there is progressive disease, change antibiotics.
	  o If the patient is febrile after 5 days, consider adding an antifungal drug

Clinical Guideline	Recommendation(s)
	Antibiotic Prophylaxis for Afebrile Neutropenic Patients • Use of antibiotic prophylaxis is not routine because of emerging antibiotic resistance, except for the use of trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* pneumonitis.
Surgical Infection Prevention Guideline Writers Workgroup (SIPGWW): **Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project**[141] **(2004)**	General Considerations • There is published evidence to support the use of many prophylactic antimicrobial regimens besides those included in this advisory statement or in existing guidelines. • Factors such as cost, half-life, safety, and antimicrobial resistance favor the use of older agents with a relatively narrow spectrum. • The use of newer, broad-spectrum drugs that are front-line therapeutic agents should be avoided in surgical prophylaxis to reduce emergence of bacterial strains that are resistant to these antimicrobials. Gynecologic and Obstetrical Surgery • For abdominal or vaginal hysterectomy, cefotetan is preferred, but reasonable alternatives are cefazolin and cefoxitin. In cases of β-lactam allergy, the workgroup recommends the use of one of the following regimens: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; metronidazole combined with gentamicin or ciprofloxacin; or clindamycin monotherapy. A single 750-mg dose of levofloxacin can be substituted for ciprofloxacin. • For cesarean section, a narrow-spectrum antimicrobial regimen similar to that recommended for hysterectomy provides adequate prophylaxis. Orthopedic Total Joint (Hip and Knee) Arthroplasty • The preferred antimicrobials for prophylaxis in patients undergoing hip or knee arthroplasty are cefazolin and cefuroxime. • Vancomycin or clindamycin may be used in patients with serious allergy or adverse reactions to β-lactams. Cardiothoracic and Vascular Surgery • The recommended antimicrobials for cardiothoracic and vascular operations include cefazolin or cefuroxime. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin is appropriate, and clindamycin may be an acceptable alternative. Colorectal Surgery • Antimicrobial prophylaxis for colorectal operations can consist of an orally administered antimicrobial bowel preparation, a preoperative parenteral antimicrobial, or the combination of both. • Recommended oral prophylaxis consists of neomycin plus erythromycin or neomycin plus metronidazole, initiated no more than 18–24 h before the operation, along with administration of a mechanical bowel preparation. • Cefotetan or cefoxitin are recommended for parenteral prophylaxis, and the combination of parenteral cefazolin and metronidazole is also recommended as an alternative. • For patients with confirmed allergy or adverse reaction to β-lactams, use of one of the following regimens is recommended: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; or metronidazole combined with gentamicin or ciprofloxacin. A single 750-mg dose of levofloxacin can be substituted for ciprofloxacin.
American College of Gastroenterology (ACG): **Practice Guidelines: Hepatic Encephalopathy**[144] **(2001)**	Bowel Cleansing • Bowel cleansing is a standard therapeutic measure in hepatic encephalopathy. • Colonic cleansing reduces the luminal content of ammonia, decreases colonic bacterial counts, and lowers blood ammonia in cirrhotic

Clinical Guideline	Recommendation(s)
	patients. • Various laxatives may be used, but nonabsorbable disaccharides are preferred. • Alternatively, bowel cleansing can also be achieved after irrigation of the gut with isotonic solution of mannitol. <u>Nonabsorbable Disaccharides</u> • Lactulose is a first-line treatment of hepatic encephalopathy. • For acute encephalopathy, lactulose 45 ml is followed by dosing every hour until evacuation occurs. Then dosing is adjusted to achieve two to three soft bowel movements per day (15–45 ml every 8–12 hours). <u>Antibiotics</u> • Antibiotics are a therapeutic alternative to nonabsorbable disaccharides for the treatment of acute and chronic encephalopathy and cirrhosis. • For acute encephalopathy, neomycin (3–6 g/day) should be given for 1-2 weeks. • For chronic encephalopathy, neomycin (1–2 g/day) should be given. Neomycin can be combined with oral lactulose in problematic cases. • Metronidazole should be started at a dose of 250 mg twice daily.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antibacterials are noted in Tables 5-6. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 5. FDA-Approved Indications for the Antibacterials, Miscellaneous (Drugs B-L)[1-17]

Indication	Bacitracin	Bismuth/ Metronidazole/ Tetracycline	Clindamycin	Colistimethate	Daptomycin	Lincomycin
Dermatological Infections						
Skin and skin-structure infections			✔ *§		✔	
Gastrointestinal Infections						
Treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori* (in combination with an H_2 antagonist)		✔ †				
Treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori* (in combination with omeprazole)		✔ ‡				
Genitourinary Infections						
Endometritis			✔ *§			
Gynecologic infections			✔ *§			
Nongonococcal tubo-ovarian abscess			✔ *§			
Pelvic cellulitis			✔ *§			
Postsurgical vaginal cuff infection			✔ *§			
Respiratory Infections						
Empyema	✔		✔ *§			
Lung abscess			✔ *§			
Pneumonia	✔		✔ §			
Pneumonitis			✔ *			
Respiratory tract infection			✔ *§			
Miscellaneous Infections						
Bone and/or joint infections			✔ §			
Endocarditis					✔	
Intra-abdominal infections			✔ *§			
Septicemia			✔ *		✔	
Serious infections due to susceptible organisms				✔		✔

†Helidac® only
§Injection formulation
*Oral formulation
‡Pylera® only

Table 6. FDA-Approved Indications for the Antibacterials, Miscellaneous (Drugs L-V)[1-17]

Indication	Linezolid	Polymyxin B Sulfate	Quinupristin/ Dalfopristin	Rifaximin	Telavancin	Vancomycin
Central Nervous System Infections						
Meningeal infections		✔				
Dermatological Infections						
Diabetic foot infections	✔					
Skin and skin-structure infections	✔		✔		✔	✔ §
Gastrointestinal Infections						
Enterocolitis						✔ *
Pseudomembranous colitis due to *C. difficile*						✔ *
Travelers' diarrhea				✔		
Urinary tract infections		✔				
Respiratory Infections						
Pneumonia (community-acquired)	✔					
Pneumonia (nosocomial)	✔					
Respiratory tract infections (lower)						✔ §
Miscellaneous Infections						
Bone and/or joint infections						✔ §
Endocarditis						✔ §
Hepatic encephalopathy				✔		
Septicemia		✔				✔ §
Serious infections due to susceptible organisms		✔				✔ §
Vancomycin-resistant *Enterococcus faecium* infections	✔					

§Injection formulation
*Oral formulation

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antibacterials are listed in Table 7.

Table 7. Pharmacokinetic Parameters of the Antibacterials, Miscellaneous[1-17]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Bacitracin	Not reported	Not reported	Not reported	Renal (10-40)	Not reported
Bismuth	<1	>90	Not reported	Renal	21-72 days
Clindamycin	Oral: 90	60-95	Liver	Renal (10) Feces (4)	2-4
Colistimethate	Not reported	Not reported	Not reported	Renal (60)	2-3
Dalfopristin	Not reported	Not reported	Not reported	Renal (19)	0.70
Daptomycin	Not reported	90-93	Not reported	Renal (78) Feces (6)	7.7-8.3
Lincomycin	Not reported	Not reported	Liver	Renal (2-30)	5
Linezolid	100	31	Liver	Renal (30) Feces (9)	Oral: 4.3-5.4 IV: 4.4-4.8
Metronidazole	Not reported	<20	Liver (30-60)	Renal (60-80) Feces (6-15)	6-8
Polymyxin B sulfate	Not reported	79-92	Not reported	Renal (<1)	6
Quinupristin	Not reported	Not reported	Not reported	Renal (15) Feces (75-77)	0.85
Rifaximin	Not reported	68	Not reported	Renal (<1) Feces (97)	2-5
Telavancin	Not reported	90	Not reported	Renal (76)	6.6-9.6
Tetracycline	75	65	Not reported	Renal (60)	8-11
Vancomycin	IV: 38	50	Not reported	IV: Renal (80-90)	4-6

V. Drug Interactions

Significant drug interactions with the miscellaneous antibacterials are listed in Table 8.

Table 8. Significant Drug Interactions with the Antibacterials, Miscellaneous[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Bismuth subsalicylate	1	Anticoagulants	The risk of bleeding, particularly gastrointestinal, may be increased by coadministration of anticoagulants with bismuth.
Bismuth subsalicylate	1	Methotrexate	Bismuth may inhibit renal excretion of methotrexate and displace it from plasma protein binding sites. Bismuth may increase plasma concentrations of methotrexate with an increased risk of bone marrow and hepatic toxicity
Daptomycin	1	Statins	Coadministration of daptomycin and statins may increase the risk of rhabdomyolysis. The mechanism for this interaction is currently unknown.
Linezolid	1	Anorexiants	Toxicity of anorexiants may be

Generic Name(s)	Significance Level	Interaction	Mechanism
			increased by coadministration of linezolid. Headache, hyperpyrexia, elevated blood pressure, and bradycardia may occur. Anorexiants can liberate large quantities of intraneuronal norepinephrine that have accumulated during treatment with linezolid.
Linezolid	1	Bupropion	Use of bupropion with linezolid is contraindicated due to the potential for hypertensive crisis. The inhibitory effects of bupropion on norepinephrine and dopamine reuptake may be enhanced by concomitant use of linezolid.
Linezolid	1	Buspirone	The risk of linezolid-induced hypertension may be increased by coadministration of buspirone. The mechanism for this interaction is currently unknown.
Linezolid	1	Cyclobenzaprine	Cyclobenzaprine is a tricyclic amine structurally related to tricyclic antidepressants. Though the mechanism of action is unknown, it is likely that adrenergic activity is enhanced with concurrent administration.
Linezolid	1	Dextromethorphan	A severe and potentially fatal toxic reaction may occur when dextromethorphan is administered to patients receiving linezolid. The mechanism for this interaction is currently unknown.
Linezolid	1	Levodopa	Linezolid may decrease the enzymatic degradation of dopamine and norepinephrine formed from levodopa.
Linezolid	1	Meperidine	A severe and potentially fatal reaction may occur shortly after administering meperidine to patients receiving linezolid. The excitatory interaction may be due to additive increases of central nervous system serotonin activity. The depressive form may result from inhibition of hepatic metabolism of meperidine.
Linezolid	1	Methylphenidate	Pharmacologic effects of methylphenidate may be increased by linezolid. Headache, GI symptoms and hypertension may occur.
Linezolid	1	Nefazodone	Unexpected toxicity may occur in some patients. The mechanism for this interaction is currently

Generic Name(s)	Significance Level	Interaction	Mechanism
			unknown.
Linezolid	1	Norepinephrine reuptake inhibitors	Toxic effects may be increased with concurrent administration of norepinephrine reuptake inhibitors and linezolid. Serious and sometimes fatal reactions have occurred. Pharmacologic effects of norepinephrine reuptake inhibitors and linezolid may be additive.
Linezolid	1	Serotonin reuptake blockers	Serotonin reuptake blockers and linezolid increase central nervous system serotonin activity, perhaps synergistically. This may cause central nervous system toxicity.
Linezolid	1	SNRI's	Linezolid and SNRI's may exert additive pharmacologic activity potentially leading to severe central nervous system toxicity.
Linezolid	1	Sympathomimetics	Pharmacologic effects of sympathomimetics may be increased by linezolid. Headache, hyperpyrexia, and hypertension may occur. The mechanism differs depending on the type of sympathomimetics involved.
Linezolid	1	Tetracyclic antidepressants	The mechanism is unknown. Tetracyclic antidepressants are thought to act by blocking reuptake of neurotransmitters, including norepinephrine. The concomitant use of monoamine oxidase inhibitors could potentiate sympathomimetic activity.
Linezolid	1	Tramadol	A severe reaction potentially involving the respiratory, cardiovascular, and central nervous systems may occur shortly after administering tramadol to patients receiving linezolid. The seizure threshold may also be reduced.
Linezolid	1	Trazodone	Linezolid and trazodone may increase central nervous system serotonin activity, perhaps synergistically.
Linezolid	1	Tricyclic antidepressants	Severe, sometimes lethal, toxicity may occur. The mechanism for this interaction in currently unknown.
Linezolid	1	Triptans	Inhibition of monoamine oxidase by linezolid may decrease the metabolic elimination of triptans. Other mechanisms may exist. The potential for development of serotonin syndrome is a possibility.
Metronidazole	1	Anticoagulants	The anticoagulant effect of warfarin may be enhanced and hemorrhage could occur due to decreased

Generic Name(s)	Significance Level	Interaction	Mechanism
			metabolism of warfarin by metronidazole.
Metronidazole	1	Busulfan	Busulfan trough concentrations may be elevated, increasing risk of serious toxicity. Avoid coadministration of busulfan and metronidazole.
Metronidazole	1	Disulfiram	Acute toxic psychosis may occur during the coadministration of metronidazole and disulfiram.
Metronidazole	1	Ergot derivatives	Metronidazole and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative and serious toxicity.
Quinupristin-Dalfopristin	1	Methadone	Methadone inhibits cardiac potassium channels and prolongs the QT interval. This may become significant with larger doses and in combination with other drugs that may also prolong the QT interval, such as quinupristin-dalfopristin.
Tetracyclines	1	Acitretin	Concurrent administration of acitretin and tetracycline may increase the risk for development of pseudotumor cerebri. The mechanism for this interaction is unknown.
Tetracyclines	1	Anticoagulants	Hypoprothrombinemic effects of anticoagulants may be increased by Tetracycline. Bleeding may occur.
Tetracyclines	1	Isotretinoin	Concurrent administration of isotretinoin and tetracycline may increase the risk of pseudotumor cerebri. The mechanism of this interaction is unknown.
Bacitracin	2	Non-depolarizing muscle relaxants	Neuromuscular blockage may be enhanced. The polypeptide antibiotics may affect pre-synaptic and post-synaptic myoneural function and act synergistically with nondepolarizing muscle relaxants.
Bismuth subsalicylate	2	Sulfinpyrazone	The uricosuric effect of sulfinpyrazone may be decreased by bismuth.
Bismuth subsalicylate	2	Valproic acid	Pharmacologic effects of valproic acid may be increased by bismuth. Both displacement from plasma protein binding sites and decreased total body clearance have been suggested as mechanisms.
Clindamycin	2	Non-depolarizing muscle relaxants	The neuromuscular blocking effects of non-depolarizing muscle

Generic Name(s)	Significance Level	Interaction	Mechanism
			relaxants may be increased by clindamycin. The mechanism is through additive or synergistic pharmacologic activity.
Clindamycin, lincomycin	2	Aluminum salts	Gastrointestinal absorption is decreased for lincomycin and delayed for clindamycin when they are administered with kaolin-pectin antidiarrheals.
Clindamycin, lincomycin	2	Nondepolarizing muscle relaxants	The lincosamides may enhance the actions of the nondepolarizing muscle relaxants, possibly contributing to profound and severe respiratory depression.
Colistimethate	2	Non-depolarizing muscle relaxants	Neuromuscular blockage may be enhanced. The polypeptide antibiotics may affect pre-synaptic and post-synaptic myoneural function and act synergistically with nondepolarizing muscle relaxants.
Linezolid	2	Apraclonidine	Hypertension may be potentiated. The mechanism is unknown.
Linezolid	2	β-2 agonists	Coadministration of linezolid and β-2 agonists may result in adverse cardiovascular effects characterized by hypertension. Inhibition of monoamine oxidase by linezolid may result in reversible enhancement of the pressor response with concomitant administration of β-2 agonists.
Linezolid	2	COMT inhibitors	The combination of linezolid with COMT inhibitors may result in inhibition of the majority of pathways responsible for normal catecholamine metabolism.
Linezolid	2	MAOI's	Adverse effects may be increased with concurrent administration of linezolid and MAOIs.
Linezolid	2	Narcotic analgesics	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering narcotic analgesics to patients receiving linezolid.
Linezolid	2	Sibutramine	Use of high-dose sibutramine with linezolid has been reported by the manufacturer of sibutramine to increase the potential risk for serotonin syndrome.
Linezolid	2	Tetrabenazine	The combination of linezolid and tetrabenazine may produce severe unexpected toxicity.
Linezolid	2	Tryptophan	The combination of linezolid and tryptophan may produce severe

Generic Name(s)	Significance Level	Interaction	Mechanism
			unexpected toxicity in some patients.
Metronidazole	2	Barbiturates	Therapeutic failure of metronidazole may result from barbiturate induction of metronidazole metabolism resulting in more rapid elimination and lower serum concentrations.
Metronidazole	2	HIV protease inhibitors	Coadministration of metronidazole and HIV protease inhibitors may cause an alcohol intolerance reaction. The alcohol and aldehyde dehydrogenase-mediated metabolic pathway of propylene glycol or alcohol, an excipient in HIV protease inhibitors, may be blocked by metronidazole.
Polymyxin B Sulfate	2	Non-depolarizing muscle relaxants	Neuromuscular blockage may be enhanced. The polypeptide antibiotics may affect pre-synaptic and post-synaptic myoneural function and act synergistically with nondepolarizing muscle relaxants.
Quinupristin-dalfopristin	2	Cisapride	Pharmacologic and toxic effects of cisapride may be increased by quinupristin-dalfopristin. Inhibition of cytochrome P450 3A4 isoenzymes by quinupristin-dalfopristin may decrease the metabolic elimination of cisapride.
Quinupristin-dalfopristin	2	Cyclosporine	Pharmacologic and toxic effects of cyclosporine may be increased by quinupristin-dalfopristin. Inhibition of cytochrome P450 3A4 isoenzymes by quinupristin-dalfopristin may decrease the metabolic elimination of cyclosporine.
Quinupristin-dalfopristin	2	Macrolide immunosuppressives	Pharmacologic and toxic effects of macrolide immunosuppressives may be increased by quinupristin-dalfopristin. Inhibition of cytochrome P450 3A4 isoenzymes by quinupristin-dalfopristin may decrease the metabolic elimination of macrolide immunosuppressives.
Quinupristin-dalfopristin	2	QT prolonging agents	Inhibition of cytochrome P450 3A4 isoenzymes by quinupristin-dalfopristin may decrease the metabolic elimination of QT-prolonging agents. QT-prolonging agents and quinupristin-dalfopristin may cause additive QT interval prolongation.
Quinupristin-	2	Statins	Pharmacologic and toxic effects of

Generic Name(s)	Significance Level	Interaction	Mechanism
dalfopristin			statins may be increased by quinupristin-dalfopristin. Inhibition of cytochrome P450 3A4 isoenzymes by quinupristin-dalfopristin may decrease the metabolic elimination of statins.
Quinupristin-dalfopristin	2	Vinca alkaloids	Pharmacologic and toxic effects of vinca alkaloids may be increased by quinupristin-dalfopristin. Inhibition of cytochrome P450 3A4 isoenzymes by quinupristin-dalfopristin may decrease the metabolic elimination of vinca alkaloids.
Tetracyclines	2	Aluminum salts	The antimicrobial effectiveness of tetracycline may be decreased by aluminum salts. Oral and enterohepatic absorption of tetracycline may be decreased due to formation of poorly soluble chelates with aluminum.
Tetracyclines	2	Atovaquone	Reduced oral absorption of atovaquone may occur due to a disruption of the gastrointestinal tract caused by tetracycline.
Tetracyclines	2	Calcium salts	The antimicrobial effectiveness of tetracycline may be decreased by calcium salts. The gastrointestinal absorption of tetracycline may be decreased due to formation of a poorly soluble chelate with calcium.
Tetracyclines	2	Digoxin	The bioavailability of digoxin may be increased in some patients by tetracycline due to an alteration in the gastrointestinal flora.
Tetracyclines	2	Iron salts	Iron salts impair gastrointestinal absorption and decrease the antimicrobial effectiveness of tetracycline. Hematologic response to iron salts may be impaired by tetracycline.
Tetracyclines	2	Magnesium salts	The antimicrobial effectiveness of tetracycline may be decreased by magnesium salts. Magnesium salts decrease gastrointestinal absorption of tetracycline due to formation of poorly soluble chelates.
Tetracyclines	2	Methoxyflurane	The nephrotoxic effects of methoxyflurane may be increased by tetracycline. The mechanism of this interaction is unknown.
Tetracyclines	2	Oral contraceptives	Pharmacologic effects of contraceptives may be decreased by tetracycline in a small unidentifiable subpopulation of

Generic Name(s)	Significance Level	Interaction	Mechanism
			patients. Breakthrough bleeding and pregnancy may occur. Tetracycline may alter gut flora and/or cause other GI disturbances (vomiting and diarrhea). Lower plasma concentrations of certain contraceptive steroids may result.
Tetracyclines	2	Penicillins	The antimicrobial effectiveness of penicillins may be decreased by tetracycline.
Tetracyclines	2	Urinary alkalinizers	The antimicrobial effectiveness of tetracycline may be decreased by urinary alkalinizers.
Tetracyclines	2	Zinc salts	The antimicrobial effectiveness of tetracycline may be decreased by zinc salts. The gastrointestinal absorption of tetracycline is decreased due to formation of a poorly soluble chelate with zinc.
Vancomycin	2	Indomethacin and derivatives	Pharmacologic and toxic effects of vancomycin may be increased by indomethacin and derivatives in neonates. The mechanism is unknown.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antibacterials are listed in Tables 9-10. The boxed warnings for bacitracin, clindamycin, lincomycin, metronidazole, polymyxin B sulfate, quinupristin/dalfopristin and telavancin are listed in Tables 11-17.

Table 9. Adverse Drug Events (%) Reported with the Antibacterials, Miscellaneous (Drugs B-L)[1-17]

Adverse Events	Bacitracin	Bismuth/ Metronidazole/ Tetracycline	Clindamycin	Colistimethate	Daptomycin	Lincomycin
Cardiovascular						
Atrial fibrillation	-	-	-	-	<1	-
Atrial flutter	-	-	-	-	<1	-
Cardiac arrest	-	-	✔	-	<1	-
Cardiopulmonary arrest	-	-	✔	-	-	✔
Cerebral ischemia	-	<1	-	-	-	-
Chest pain	-	1	-	-	7	-
Edema	✔	-	-	-	7	-
Flattening T-wave	-	✔	-	-	-	-
Hypertension	-	<1	-	-	1-6	-
Hypotension	✔	-	✔	-	2-5	✔
Myocardial infarction	-	<1	-	-	-	-
Palpitation	-	1	-	-	-	-
Central Nervous System						
Anxiety	-	1	-	-	5	-
Ataxia	-	✔	-	-	-	-
Bulging fontanelle	-	✔	-	-	-	-
Depression	-	✔	-	-	-	-
Dizziness	-	✔	-	✔	2-6	✔
Fatigue	-	-	-	-	<1	-
Fever	✔	✔	-	✔	2-7	-
Hallucinations	-	-	-	-	<1	-
Headache	-	✔	-	✔	5-7	-
Incoordination	-	✔	-	-	-	-
Insomnia	-	1	-	-	5-9	-
Irritability	-	✔	-	-	-	-
Malaise	-	<1	-	-	-	-
Mental status change	-	-	-	-	<1	-
Myasthenic syndrome	-	✔	-	-	-	-
Nervousness	-	<1	-	-	-	-

Adverse Events	Bacitracin	Bismuth/ Metronidazole/ Tetracycline	Clindamycin	Colistimethate	Daptomycin	Lincomycin
Paresthesia	-	-	-	✔	<1	-
Peripheral neuropathy	-	✔	-	-	-	-
Pseudotumor cerebri	-	✔	-	-	-	-
Seizure	-	✔	-	✔	-	-
Somnolence	-	<1	-	-	-	-
Syncope	-	<1	-	-	-	-
Tingling of extremities	✔	-	-	✔	-	-
Tinnitus	-	✔	-	-	<1	✔
Vertigo	-	✔	-	-	-	✔
Visual disturbances	-	✔	-	-	-	-
Weakness	-	✔	-	✔	-	-
Dermatologic						
Acne	-	<1	-	-	-	-
Anaphylactoid purpura	-	✔	-	-	-	-
Discoloration of nails	-	✔	-	-	-	-
Ecchymosis	-	<1	-	-	-	-
Eczema	-	-	-	-	<1	-
Erythema	-	-	-	-	5	-
Erythema multiforme	-	-	✔	-	-	✔
Exfoliative dermatitis	-	✔	✔	-	-	✔
Flushing	-	-	-	-	<1	-
Heat rash	-	-	-	-	<1	-
Photosensitivity	-	<1	-	-	-	-
Pruritus	✔	<1	✔	✔	3-6	✔
Rash	✔	<1	✔	✔	4-7	✔
Stevens-Johnson syndrome	-	-	✔	-	-	✔
Urticaria	-	✔	✔	✔	-	✔
Vesiculobullous dermatitis	-	-	-	-	-	✔
Gastrointestinal						
Abdominal cramping	-	✔	-	-	-	-
Abdominal distention	-	-	-	-	<1	-
Abdominal pain	-	✔	✔	-	6	✔
Anal discomfort	-	✔	-	-	-	-
Anorexia	✔	2	-	-	-	-
Appetite decreased	✔	-	-	-	<1	-
Black stool	-	✔	-	-	-	-

Adverse Events	Bacitracin	Bismuth/ Metronidazole/ Tetracycline	Clindamycin	Colistimethate	Daptomycin	Lincomycin
Colitis	-	-	✔	-	-	✔
Constipation	-	2	-	-	6-11	-
Diarrhea	✔	✔	✔	-	5-12	✔
Discoloration of teeth	-	✔	-	-	-	-
Discoloration of tongue	-	2	-	-	-	-
Dry mouth	-	1	-	-	<1	-
Duodenal ulcer	-	1	-	-	-	-
Dyspepsia	-	✔	-	-	1-4	-
Dysphagia	-	<1	-	-	<1	-
Enamel hypoplasia	-	✔	-	-	-	-
Enterocolitis	-	✔	-	-	-	✔
Epigastric distress	-	✔	-	-	<1	-
Eructation	-	<1	-	-	-	-
Esophageal ulceration	-	✔	-	-	-	-
Esophagitis	-	✔	✔	-	-	-
Extraintestinal cancer	-	✔	-	-	-	-
Flatulence	-	<1	-	-	<1	-
Gastrointestinal hemorrhage	-	1	-	-	2	-
Gastrointestinal upset	✔	-	-	✔	✔	-
Gingival pain	-	-	-	-	<1	-
Glossitis	-	<1	-	-	-	✔
Intestinal obstruction	-	<1	-	-	-	-
Loose stools	-	-	-	-	4	-
Melena	-	3	-	-	-	-
Nausea	✔	12	✔	-	6-10	✔
Oral moniliasis	-	✔	-	-	-	-
Pseudomembranous colitis	-	-	✔	-	-	✔
Rectal hemorrhage	-	<1	-	-	-	-
Rectal itching/burning	✔	-	-	-	-	✔
Stomatitis	-	<1	-	-	<1	✔
Stool abnormality	-	1	-	-	-	-
Taste alteration	-	1	✔	-	<1	-
Tooth disorder	-	<1	-	-	-	-
Vomiting	✔	✔	✔	-	3-12	✔
Genitourinary						
Abnormal kidney function	✔	-	✔	✔	<1	✔

Adverse Events	Bacitracin	Bismuth/ Metronidazole/ Tetracycline	Clindamycin	Colistimethate	Daptomycin	Lincomycin
Acute kidney failure	-	-	-	-	2-3	-
Dysuria	-	✔	-	-	-	-
Incontinence	-	✔	-	-	-	-
Urinary tract infections	-	<1	-	-	2-7	-
Vaginitis	-	4	✔	-	-	✔
Hematologic						
Agranulocytosis	-	-	✔	-	-	✔
Anemia	-	-	-	-	2-13	✔
Bone marrow toxicity	✔	-	-	-	-	✔
Eosinophilia	-	-	✔	-	2	-
Leukocytosis	-	-	-	-	<1	-
Leukopenia	-	-	✔	-	-	✔
Neutropenia	-	-	✔	-	-	✔
Pancytopenia	-	-	-	-	-	✔
Thrombocythemia	-	-	-	-	<1	-
Thrombocytopenia	-	-	✔	-	<1	✔
Thrombocytosis	-	-	-	-	<1	-
Hepatic						
Jaundice	-	-	✔	-	<1	✔
Laboratory Test Abnormalities						
Abnormal liver function tests	-	-	✔	-	1-3	✔
ALT increased	-	✔	-	-	2-3	2-10
Alkaline phosphatase increased	-	-	-	-	2	1-4
AST increased	-	✔	-	-	2-3	2-5
BUN increased	-	-	-	✔	-	-
Electrolyte disturbance	-	-	-	-	<6	-
Hyperbilirubinemia	-	-	-	-	-	<1
INR increased	-	-	-	-	2	-
Phosphorus increased	-	-	-	-	2	-
Prothrombin time prolonged	-	-	-	-	<1	-
Serum creatinine increased	-	-	-	✔	3-7	-
Serum lactate dehydrogenase increased	-	-	-	-	<1	-
Musculoskeletal						
Arthralgia	-	-	-	-	1-3	-
Arthritis	-	✔	-	-	-	-

Adverse Events	Bacitracin	Bismuth/ Metronidazole/ Tetracycline	Clindamycin	Colistimethate	Daptomycin	Lincomycin
Back pain	-	2	-	-	7	-
Muscle cramps/weakness	-	-	-	-	<1	-
Myalgia	-	-	-	-	<1	-
Rheumatoid arthritis	-	<1	-	-	-	-
Tendonitis	-	<1	-	-	-	-
Weakness	-	4	-	-	5	-
Respiratory						
Apnea	-	-	-	✔	-	-
Cough	-	<1	-	-	3	-
Dyspnea	-	-	-	-	2-3	-
Pharyngitis	-	2	-	-	-	-
Pharyngolaryngeal pain	-	-	-	-	8	-
Pleural effusion	-	-	-	-	6	-
Pneumonia	-	-	-	-	3	-
Polyarthritis	-	-	✔	-	-	-
Respiratory arrest	✔	-	-	✔	-	-
Rhinitis	-	1	-	-	-	-
Upper respiratory tract infection	-	2	-	-	-	-
Other						
Anaphylaxis	✔	✔	✔	-	<1	✔
Angioedema	-	-	-	-	-	✔
Angioneurotic edema	-	✔	-	-	-	-
Asthenia	-	-	-	-	5	-
Ataxia	-	-	-	✔	-	-
Bacteremia	-	-	-	-	5	-
Blurred vision	-	-	-	-	<1	-
Conjunctivitis	-	<1	-	-	-	-
Dyskinesia	-	-	-	-	<1	-
Flu syndrome	-	✔	-	-	-	-
Fungal infections	-	-	-	-	2-3	-
Hypoesthesia oral	-	-	-	-	<1	-
Injection site reactions	-	-	✔	-	3-6	-
Jitteriness	-	-	-	-	<1	-
Limb pain	-	-	-	-	2-9	-
Lymphadenopathy	-	-	-	-	<1	-
Neoplasm	-	<1	-	-	-	-

Adverse Events	Bacitracin	Bismuth/ Metronidazole/ Tetracycline	Clindamycin	Colistimethate	Daptomycin	Lincomycin
Neuromuscular blockade	✔	-	-	-	-	-
Osteomyelitis	-	-	-	-	6	-
Pain	✔	✔	-	-	-	-
Pain at injection site	✔	-	✔	-	-	✔
Rigors	-	-	-	-	<1	-
Sepsis	-	-	-	-	5	-
Serum sickness-like reaction	-	-	-	-	-	✔
Sinusitis	-	✔	-	-	-	-
Slurred speech	-	-	-	✔	-	-
Sweating increased	✔	-	-	-	5	-
Thrombophlebitis	-	-	✔	-	-	-

✔ Percent not specified
- Event not reported

Table 10. Adverse Drug Events (%) Reported with the Antibacterials, Miscellaneous (Drugs L-V)[1-17]

Adverse Events	Linezolid	Polymyxin B Sulfate	Quinupristin/ Dalfopristin	Rifaximin	Telavancin	Vancomycin
Cardiovascular						
Cardiac arrest	-	-	<1	-	-	-
Chest pain	-	-	-	>2-5	-	-
Edema	✔	-	17-18	15	-	-
Hypertension	<1	-	-	-	-	-
Hypotension	-	-	-	>2-5	-	✔
Pericarditis	-	-	<1	-	-	-
Shock	-	-	<1	-	-	-
Central Nervous System						
Abnormal dreams	-	-	-	<2	-	-
Ataxia	-	✔	-	-	-	-
Chills	-	-	-	-	-	✔
Confusion	-	-	-	>2-5	-	-
Depression	-	-	-	7	-	-
Dizziness	<2	✔	-	13	6	✔
Drowsiness	-	✔	-	-	-	-
Dysautonomia	-	-	<1	-	-	-
Encephalopathy	-	-	<1	-	-	-

Adverse Events	Linezolid	Polymyxin B Sulfate	Quinupristin/ Dalfopristin	Rifaximin	Telavancin	Vancomycin
Fatigue	-	-	-	12	-	-
Fever	2	-	-	6	-	✔
Headache	1-11	-	2	10	11	-
Insomnia	3	-	-	13	13	-
Irritability	-	✔	-	-	-	-
Meningeal signs	✔	-	-	-	-	-
Migraine	-	-	-	<2	-	-
Neuropathy	-	-	<1	-	-	-
Paresthesia	-	✔	<1	-	-	-
Peripheral neuropathy	<1	-	-	-	5	-
Seizure	<1	-	<1	-	-	-
Syncope	-	-	<1	<2	-	-
Tinnitus	-	-	-	<2	-	✔
Tremor	-	-	-	>2-5	-	-
Dermatologic						
Photosensitivity	-	-	-	<2	-	-
Pruritus	<1	-	2	9	36	✔
Rash	2	✔	3	5	4	✔
Stevens-Johnson syndrome	<1	-	-	-	-	✔
Urticaria	-	-	<1	-	-	✔
Gastrointestinal						
Abdominal distention	-	-	-	<2	-	-
Abdominal pain	✔	-	-	>2-9	2	-
Anorexia	-	-	-	>2-5	-	-
Appetite decrease	-	-	-	-	3	-
Blood in stool	-	-	-	<2	-	-
Constipation	2	-	-	3	-	-
Defecation urgency	-	-	-	6	-	-
Diarrhea	3-11	-	3	<2	7	-
Dry mouth	-	-	-	>2-5	-	-
Dyspepsia	<1	-	-	-	-	-
Fecal abnormality	-	-	-	<2	-	-
Flatulence	-	-	-	11	-	-
Gastrointestinal upset	-	-	-	<2	-	-
Gingival disorder	-	-	-	<2	-	-
Inguinal hernia	-	-	-	<2	-	-
Nausea	3-10	-	3-5	14	27	✔

Adverse Events	Linezolid	Polymyxin B Sulfate	Quinupristin/ Dalfopristin	Rifaximin	Telavancin	Vancomycin
Oral moniliasis	<1	-	-	-	-	-
Pancreatitis	✔	-	<1	-	-	-
Pseudomembranous colitis	-	-	-	-	-	✔
Stomatitis	-	-	<1	-	-	-
Taste alteration	1	-	-	<2	33	-
Tongue discoloration	<1	-	-	-	-	-
Vomiting	1-4	-	3-4	2	14	✔
Weight decreased	-	-	-	<2	-	-
Genitourinary						
Abnormal kidney function	-	✔	-	<2	-	✔
Acute kidney failure	-	-	-	-	-	✔
Albuminuria	-	✔	-	-	-	-
Choluria	-	-	-	<2	-	-
Cylindruria	-	✔	-	-	-	-
Dysuria	-	-	-	<2	-	-
Hematuria	-	✔	<1	<2	-	-
Leukocyturia	-	✔	-	-	-	-
Pyuria	-	-	-	<2	-	-
Vaginitis	-	-	<1	-	-	-
Hematologic						
Agranulocytosis	-	-	-	-	-	✔
Anemia	✔	-	-	8	-	-
Eosinophilia	✔	✔	-	-	-	✔
Hemolytic anemia	-	-	<1	-	-	-
Leukopenia	1-2	-	-	-	-	-
Lymphocytosis	-	-	-	<2	-	-
Monocytosis	-	-	-	<2	-	-
Neutropenia	<1	-	-	<2	-	✔
Pancytopenia	<1	-	<1	-	-	-
Thrombocytopenia	1-10	-	<1	-	7	✔
Laboratory Test Abnormalities						
Abnormal liver function tests	1	-	-	-	-	-
AST increased	-	-	-	<2	-	-
BUN increased	<2	-	-	-	-	✔
Hyperbilirubinemia	-	-	3-35	-	-	-
Hypoglycemia	-	-	-	>2-5	-	-
Serum creatinine increased	<1	-	-	-	8	✔

Adverse Events	Linezolid	Polymyxin B Sulfate	Quinupristin/ Dalfopristin	Rifaximin	Telavancin	Vancomycin
Musculoskeletal						
Arthralgia	-	-	≤47	6	-	-
Myalgia	-	-	≤47	>2-5	-	-
Myasthenia	-	-	<1	-	-	-
Neck pain	-	-	-	<2	-	-
Neuromuscular blockade	-	✔	-	-	-	-
Weakness	-	-	-	<2	-	-
Respiratory						
Apnea	✔	-	-	-	-	-
Dyspnea	✔	✔	<1	6	8	✔
Nasal passage irritation	-	-	-	<2	-	-
Nasopharyngitis	-	-	-	7	-	-
Pharyngitis	-	-	-	<2	-	-
Pharyngolaryngeal pain	-	-	-	<2	-	-
Pleural effusion	-	-	<1	-	-	-
Pneumonia	-	-	-	>2-5	-	-
Respiratory arrest	-	✔	-	-	-	-
Respiratory distress syndrome	-	-	<1	-	-	-
Respiratory tract infection	-	-	-	<2	-	-
Rhinitis	-	-	-	>2-5	-	-
Rhinorrhea	-	-	-	<2	-	-
Upper respiratory tract infection	-	-	-	>2-5	-	-
Wheezing	-	-	-	-	-	✔
Other					-	
Allergic reaction	-	-	<1	-	-	-
Anaphylaxis	<1	✔	-	<2	-	-
Angioneurotic edema	-	-	-	<2	-	-
Ataxia	-	✔	-	-	-	-
Blurred vision	-	✔	-	-	-	-
Clamminess	-	-	-	<2	-	-
Dehydration	-	-	-	>2-5	-	-
Dry lips	-	-	-	<2	-	-
Flu syndrome	-	-	-	>2-5	-	-
Fungal infections	<1-2	-	-	-	-	-
Gout	-	-	<1	-	-	-
Hearing loss	-	-	-	-	<1	✔
Hypoesthesia oral	-	-	-	>2-5	-	-

Adverse Events	Linezolid	Polymyxin B Sulfate	Quinupristin/ Dalfopristin	Rifaximin	Telavancin	Vancomycin
Injection site reactions	-	-	12-13	-	3	-
Motion sickness	-	-	-	<2	-	-
Pain	-	-	40-44	>2-5	-	-
Pain at injection site	-	-	38-42	-	4	✔
Redman syndrome	-	-	-	-	-	✔
Rigors	-	-	-	-	4	-
Sepsis	✔	-	-	-	-	-
Thrombophlebitis	-	-	-	-	-	✔
Vasculitis	-	-	-	-	-	✔

✔ Percent not specified
- Event not reported

Table 11. Boxed Warning for Bacitracin[1]

WARNING
Nephrotoxicity: Bacitracin in parenteral (IM) therapy may cause renal failure due to tubular and glomerular necrosis. Its use should be restricted to infants with staphylococcal pneumonia and empyema when due to organisms shown to be susceptible to bacitracin. It should be used only where adequate laboratory facilities are available and when constant supervision of the patient is possible. Renal function should be carefully determined prior to and daily during therapy. The recommended daily dose should not be exceeded, and fluid intake and urinary output should be maintained at proper levels to avoid kidney toxicity. If renal toxicity occurs the drug should be discontinued. The concurrent use of other nephrotoxic drugs, particularly streptomycin, kanamycin, polymyxin B, polymyxin E (colistin), and neomycin should be avoided.

Table 12. Boxed Warning for Clindamycin[1]

WARNING
Clostridium difficile–associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*. Because clindamycin therapy has been associated with severe colitis, which may end fatally, reserve it for serious infections for which less toxic antimicrobial agents are inappropriate. Do not use clindamycin in patients with nonbacterial infections, such as most upper respiratory tract infections. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Institute appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation as clinically indicated.

Table 13. Boxed Warning for Lincomycin[1]

WARNING
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including lincomycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Because lincomycin therapy has been associated with severe colitis, which may end fatally, reserve it for serious infections for which less toxic antimicrobial agents are inappropriate. Do not use it in patients with nonbacterial infections, such as most upper respiratory tract infections. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. After the diagnosis of pseudomembranous colitis has been established, initiate therapeutic measures. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consider management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. Diarrhea, colitis, and pseudomembranous colitis may begin up to several weeks following cessation of therapy with lincomycin.

Table 14. Boxed Warning for Metronidazole[1]

WARNING
Metronidazole has been shown to be carcinogenic in mice and rats. Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions for which this drug is indicated

Table 15. Boxed Warning for the Polymyxin B Sulfate[1]

WARNING
When this drug is given IM or intrathecally, it should be given only to hospitalized patients, so as to provide constant supervision by a physician. **Nephrotoxicity:** Renal function should be carefully determined, and patients with renal damage and nitrogen retention should have reduced dosage. Patients with nephrotoxicity due to polymyxin B sulfate usually show albuminuria, cellular casts, and azotemia. Diminishing urine output and a rising blood urea nitrogen (BUN) are indications for discontinuing therapy with this drug. **Neurotoxicity:** Neurotoxic reactions may be manifested by irritability, weakness, drowsiness, ataxia, perioral paresthesia, numbness of the extremities, and blurring of vision. These are usually associated with high serum levels found in patients with impaired renal function or nephrotoxicity. **Concurrent therapy:** The concurrent or sequential use of other neurotoxic or nephrotoxic drugs with polymyxin B sulfate, particularly bacitracin, streptomycin, neomycin, kanamycin, gentamicin, tobramycin, amikacin, cephaloridine, paromomycin, viomycin, and colistin should be avoided. **Neuromuscular blockade:** The neurotoxicity of polymyxin B sulfate can result in respiratory paralysis from neuromuscular blockade, especially when the drug is given soon after anesthesia or muscle relaxants. **Use in pregnancy:** The safety of this drug in human pregnancy has not been established.

Table 16. Boxed Warning for Quinupristin/Dalfopristin[1]

WARNING
One of quinupristin/dalfopristin's approved indications is for the treatment of patients with serious or life-threatening infections associated with vancomycin-resistant *Enterococcus faecium* (VREF) bacteremia. Quinupristin/dalfopristin has been approved for marketing in the US for this indication under the FDA's accelerated approval regulations that allow marketing of products for use in life-threatening conditions when other therapies are not available. Approval of drugs for marketing under these regulations is based upon a demonstrated effect on a surrogate endpoint that is likely to predict clinical benefit. Approval of this indication is based upon quinupristin/dalfopristin's ability to clear VREF from the bloodstream with clearance of bacteremia considered to be a surrogate end point. No results from well-controlled clinical studies confirm the validity of this surrogate marker. However, a study to verify the clinical benefit of therapy with quinupristin/dalfopristin on traditional clinical endpoints (such as cure of the underlying infection) is presently underway.

Table 17. Boxed Warning for Telavancin[1]

WARNING
Fetal risk: Women of childbearing potential should have a serum pregnancy test prior to administration of telavancin. Avoid use of telavancin during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. Adverse developmental outcomes observed in 3 animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antibacterials are listed in Table 18.

Table 18. Usual Dosing Regimens for the Antibacterials, Miscellaneous[1-17]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Bacitracin	Dosing information for adults is not included in the prescribing information.	Unspecified Infections: <2,500 g: 900 units/kg/day in 2 to 3 divided doses >2,500 g: 1,000 units/kg/day in 2 to 3 divided doses	Injection: 50,000 units
Bismuth subsalicylate, metronidazole, and tetracycline	Eradication of *H. pylori*: Bismuth subsalicylate 525 mg (two 262.4 mg chewable tablets), metronidazole 250 mg (one 250 mg tablet), and tetracycline, 500 mg (one 500 mg capsule) taken 4 times daily for 14 days plus an H_2 antagonist approved for the treatment of acute duodenal ulcer	Safety and efficacy in children have not been established.	Combination package: 250-500 mg
Clindamycin	Serious Infections: Capsule: 150 to 300 mg every 6 hours Injection: 600 to 1,200 mg/day IM/IV in 2 to 4 equal doses More Severe Infections: Capsule: 300 to 450 mg every 6 hours Injection: 1,200 to 2,700 mg/day IM/IV in 2 to 4 equal doses	Serious infections: Capsule: 8 to 16 mg/kg/day divided into 3 or 4 equal doses Solution: 8 to 12 mg/kg/day divided into 3 or 4 equal doses Severe Infections: Solution: 13 to 16 mg/kg/day divided into 3 or 4 equal doses More Severe Infections: Capsule: 16 to 20 mg/kg/day divided into 3 or 4 equal doses Solution: 17 to 25 mg/kg/day divided into 3 or 4 equal doses Unspecified Infections: Neonates <1 month: Injection: 15 to 20 mg/kg/day in 3 to 4 equal doses 1 month to 16 years of age: Injection: 20 to 40 mg/kg/day in 3 to 4 equal doses	Capsule: 75 mg 150 mg 300 mg Injection: 150 mg/ml 300 mg/2 ml 600 mg/4 ml 900 mg/6 ml 600 mg/50 ml 900 mg/50 ml Solution: 75 mg/5 ml
Colistimethate	Unspecified Infections: 2.5 to 5 mg/kg per day in 2 to 4 divided doses	Unspecified Infections: 2.5 to 5 mg/kg per day in 2 to 4 divided doses	Injection: 150 mg
Colloidal bismuth subcitrate, metronidazole, and tetracycline	Eradication of *H. pylori*: 3 capsules 4 times daily for 10 days	Safety and efficacy in children have not been established.	Capsule: 125-125 mg
Daptomycin	Bacteremia:	Safety and efficacy in children	Injection:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	6 mg/kg IV once daily for 2 to 6 weeks Endocarditis: 6 mg/kg IV once daily for 2 to 6 weeks Skin and Skin-Structure Infections: 4 mg/kg IV once daily for 7 to 14 days	have not been established.	500 mg
Lincomycin	Serious Infections: 600 IM every 24 hours; 600 mg to 1 g IV every 8 to 12 hours More Severe Infections: 600 mg IM every 12 hours or more often; 600 mg to 1 g IV every 8 to 12 hours	Serious infections: >1 month of age: 10 mg/kg IM every 24 hours; 10 to 20 mg/kg IV in divided doses More Severe Infections: >1 month of age: 10 mg/kg IM every 12 hours; 10 to 20 mg/kg IV in divided doses	Injection: 300 mg/ml
Linezolid	Pneumonia (Community-Acquired): 600 mg IV/PO every 12 hours for 10 to 14 days Pneumonia (Nosocomial): 600 mg IV/PO every 12 hours for 10 to 14 days Skin and Skin-Structure Infections: Complicated: 600 mg IV/PO every 12 hours for 10 to 14 days Uncomplicated: 400 mg orally every 12 hours for 10-14 days (adults) or 600 mg orally every 12 hours (adolescents) Vancomycin-Resistant *E. faecium* Infections: 600 mg IV/PO every 12 hours for 14 to 28 days	Pneumonia (Community-Acquired): Birth to 11 years of age: 10 mg/kg IV/PO every 8 hours for 10 to 14 days ≥12 years of age: 600 mg IV/PO every 12 hours for 10 to 14 days Pneumonia (Nosocomial): Birth to 11 years of age: 10 mg/kg IV/PO every 8 hours for 10 to 14 days ≥12 years of age: 600 mg IV/PO every 12 hours for 10 to 14 days Skin and Skin-Structure Infections: Complicated: Birth to 11 years of age: 10 mg/kg IV/PO every 8 hours for 10 to 14 days ≥12 years of age: 600 mg IV/PO every 12 hours for 10 to 14 days Uncomplicated: <5 years of age: 10 mg/kg orally every 8 hours for 10 to 14 days 5 to 11 years of age: 10 mg/kg orally every 12 hours for 10 to 14 days ≥12 years of age: 600 mg orally	Injection: 200 mg/0.1 L 600 mg/300 ml Suspension: 100 mg/5 ml Tablet: 600 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		every 12 hours Vancomycin-Resistant *E. faecium* Infections: Birth to 11 years of age: 10 mg/kg IV/PO every 8 hours for 14 to 28 days ≥12 years of age: 600 mg IV/PO every 12 hours for 14 to 28 days	
Polymyxin B sulfate	Meningitis: Intrathecal: 50,000 units/day for 3 to 4 days, then every other day for ≥2 weeks after CSF cultures are negative Unspecified Infections: IM: 25,000 to 30,000 units/kg/day divided every 4 to 6 hours IV: 15,000 to 25,000 units/kg/day divided every 12 hours	Meningitis: <2 years of age: Intrathecal: 20,000 units/day for 3 to 4 days, then 25,000 units/day every other day for ≥2 weeks after CSF cultures are negative >2 years of age: Intrathecal: 50,000 units/day for 3 to 4 days, then every other day for ≥2 weeks after CSF cultures are negative Unspecified Infections: Infants: IM: up to 40,000 units/kg/day divided every 4 to 6 hours IV: up to 40,000 units/kg/day divided every 12 hours Children: IM: 25,000 to 30,000 units/kg/day divided every 4 to 6 hours IV: 15,000 to 25,000 units/kg/day divided every 12 hours	Injection: 500,000 units
Quinupristin and dalfopristin	Skin and Skin-Structure Infections: 7.5 mg/kg IV every 12 hours for at least 7 days	Skin and Skin-Structure Infections: ≥12 years of age: 7.5 mg/kg IV every 12 hours for at least 7 days	Injection: 500 mg
Rifaximin	Hepatic Encephalopathy: 550 mg twice daily Traveler's Diarrhea: 200 mg 3 times daily for 3 days	Traveler's Diarrhea: ≥12 years of age: 200 mg 3 times daily for 3 days	Tablet: 200 mg 550 mg
Telavancin	Skin and Skin-Structure Infections: 10 mg/kg IV every 24 hours for 7 to 14 days	Safety and efficacy in children have not been established.	Injection: 250 mg 750 mg
Vancomycin	Pseudomembranous Colitis and Enterocolitis: Oral: 500 mg to 2 g per day divided in 3 or 4 doses for 7 to 10 days	Pseudomembranous Colitis and Enterocolitis: Children: Oral: 40 mg/kg/day in 3 to 4 divided doses for 7 to 10 days	Capsule: 125 mg 250 mg Injection:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Unspecified Infections: Injection: 500 mg IV every 6 hours or 1 g IV every 12 hours	Unspecified Infections: <1 month of age: Injection: 15 mg/kg IV as an initial dose, followed by 10 mg/kg every 12 hours for neonates in the 1st week of life and every 8 hours thereafter up to the age of 1 month ≥1 month of age: Injection: 10 mg/kg IV per dose every 6 hours	500 mg 500 mg/0.1 L 750 mg 750 mg/0.15 L 1 g 1 g/200 ml 5 g 10 g

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antibacterials are summarized in Table 19.

Table 19. Comparative Clinical Trials with the Antibacterials, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Chen et al.[114] (2011) Clindamycin 20 mg/kg/day orally in divided doses 3 times per day for 7 days vs cephalexin 40 mg/kg/day orally in divided doses 3 times per day for 7 days	RCT Patients 6 months to 18 years of age with uncomplicated skin and soft tissue infections (SSTIs) not requiring hospitalization	N=200 3 months	Primary: Clinical improvement at 48 to 72 hours from the initiation of treatment Secondary: Resolution of disease at 7 days	Primary: A total of 94% of patients in the cephalexin group and 97% of patients in the clindamycin group showed improvement or resolution in their infection at 48 to 72 hours from the initial of treatment (P=0.50). The primary infection had worsened in 6% of patients in the cephalexin group and in 3% of patients in the clindamycin group. Secondary: A total of 97% of patients in the cephalexin group and 94% of patients in the clindamycin group had clinical resolution by 7 days (P=0.33). Only 1 patient developed a new SSTI while on therapy. Compliance with taking medications as directed was 88% in the cephalexin group and 85% in the clindamycin group (P=0.66). According to data obtained from telephone contact (73%) and chart review (100%) at the 3-month follow-up, 18% of patients had a recurrent SSTI. The risk of new SSTI did not differ according to isolation of MRSA vs MSSA from initial wound culture (21% MRSA vs 16% MSSA; P=0.51) or by cephalexin or clindamycin assignment (20% vs 16%; P=0.46). There were no serious adverse events related to study treatment.
Khawcharoenporn et al.[116] (2010) Clindamycin 300 mg 4 times per day vs	RETRO Patients ≥18 years of age with cellulitis	N=405 Variable duration	Primary: Treatment success rate, compliance, safety	Primary: The overall treatment success rate with trimethoprim-sulfamethoxazole was significantly higher than the success rate with cephalexin (91% vs 74%; P<0.001). Clindamycin success rate was higher than that of cephalexin but did not reach statistical significance (85% vs 74%; P=0.22). The success rates of trimethoprim-sulfamethoxazole and clindamycin were comparable. The treatment success rate with trimethoprim-sulfamethoxazole was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cephalexin 500 mg 4 times per day vs trimethoprim-sulfamethoxazole 1 double strength tablet twice daily				significantly more successful than cephalexin in patients who were male (P=0.001), were Pacific Islanders (P=0.001), had diabetes mellitus (P=0.001), were obese (P=0.002), had positive cultures for MRSA (P=0.01), and were cigarette smokers (P=0.04). The treatment success rate with clindamycin was higher than with cephalexin in patients who had MRSA infections (P<0.01), had moderately severe cellulitis (P<0.03), and were obese (P<0.04). Methicillin-resistant *S. aureus* was recovered in 62% of positive culture specimens. Compliance and adverse drug reaction rates were not significantly different among patients who received these 3 antibiotics. Factors associated with treatment failure included therapy with an antibiotic that was not active against community-associated MRSA (P<0.001) and severity of cellulitis (P<0.001).
Arbeit et al.[56] (2004) Daptomycin 4 mg/kg IV QD vs penicillinase-resistant penicillins (PRP), including cloxacillin, nafcillin, oxacillin, or flucloxacillin, 4-12 g IV QD in equally divided doses vs	MC, RCT (Pooled analysis) Patients aged 18-85 years with complicated skin and skin structure infections due to gram-positive organisms requiring hospitalization and parenteral therapy for ≥96 hours	N=902 Treatment: 7-14 days Follow-up: 20-28 days posttreatment	Primary: Clinical success (resolution of signs and symptoms where no further antibiotic therapy was required), relapse or new infection, or failure (if had an inadequate response)	Primary: Clinical success rate was 83.4% in the daptomycin group and 84.2% in the comparator groups (95% CI, -4 to 5.6). The response rates were comparable across baseline diagnoses. At the post-study visit, relapse or recurrence was noted in 4.2% (15/355) of patients treated with daptomycin and 5.5% (20/367) of patients that received a PRP or vancomycin (95% CI, -4.4 to 1.9). Frequency of adverse events and treatment discontinuations due to any adverse event were similar in both groups. A change to oral medication was permitted if deemed appropriate. For patients with successful outcomes receiving IV treatment alone, 63% in the daptomycin group and 33% in the comparator groups required 4 to 7 days of therapy (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vancomycin 1 g IV every 12 hours				
Pertel et al.[87] (2009) Daptomycin 4 mg/kg IV once daily for 7-14 days vs vancomycin according to standard of care for 7-14 days	RCT, SB, MC Adults diagnosed with cellulitis or erysipelas requiring hospitalization and intravenous antibiotic therapy	N=103 7-14 days	Primary: Clinical success rate	Primary: The clinical success rates were 94.0% for daptomycin and 90.2% for vancomycin (95% CI, -6.7% to 14.3%). Of the 50 patients in the daptomycin group, 36 (72.0%) were assessed as cured, 11 (22.0%) were improved and three (6.0%) had no follow-up data. Of the 51 patients in the vancomycin group, 28 (54.9%) were assessed as cured, 18 (35.3%) were improved, one (2.0%) had worsened and four (7.8%) had no follow-up data. Among the patients with cellulitis in the cSSSI studies, clinical success rates were also similar for daptomycin-treated (78.6%) and comparator-treated patients (72.7%). The mean durations of study drug administration were 6.1 days for daptomycin- and 6.2 days for vancomycin-treated patients (P=0.847). There were no significant differences between treatments in the time to achievement of any of the predefined endpoints. The median time to stabilization of infection was similar for daptomycin and vancomycin (P=0.875; 86.5 vs 85.5 hours). No differences were observed between daptomycin- and vancomycin-treated patients in the median time to defervescence (P=0.690; 12.4 vs 16.3 hours), cessation of erythema advancement (P=0.833; 21.0 vs 22.0 hours), or readiness for hospital discharge (P=0.993; 84.0 vs 85.5 hours). No differences were seen between the groups in the median time to 50% improvement for investigator-assessed composite scores (P=0.755; 39.9 vs 41.2 hours) as well as patient-reported pain (P=0.632; 37.3 vs 40.0 hours) or tightness/swelling scores (P=0.307; 31.0 vs 31.5 hours).
Davis et al.[89] (2007)	PRO, OL	N=53	Primary: Clinical resolution	Primary: The most common diagnoses were cellulitis (31%), abscess (22%), and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Daptomycin 4 mg/kg IV once daily for 3-14 days vs vancomycin historical controls	Adult patients with complicated skin and skin structure infections at risk for methicillin-resistant *Staphylococcus aureus* (MRSA) infection	14 days	and duration of therapy	both cellulitis with abscess (37%). Microbiology differed significantly between groups, with *S. aureus* found in 27 patients (51%) in the daptomycin group and 167 patients (79%) in the vancomycin group and MRSA in 22 (42%) and 159 (75%), respectively (P<0.001). The proportions of patients with clinical improvement or resolution of their infections on days 3 and 5 were 90% vs 70% and 98% vs 81% in the daptomycin vs vancomycin groups, respectively (P<0.01 for both comparisons), and 100% at the end of therapy in both groups. Among patients with complete resolution of their infections (41 patients [77%] with daptomycin vs 89 patients [42%] with vancomycin, P<0.05), median duration of intravenous therapy was 4 and 7 days, respectively, (P<0.001).
Lipsky et al.[61] (2004) Linezolid 600 mg IV/PO every 12 hours vs ampicillin-sulbactam 1.5-3 g IV every 6 hours or amoxicillin-clavulanate 500-875 mg PO every 8-12 hours	OL, MC, RCT Patients ≥18 years with diabetes mellitus and a foot infection	N=371 7-28 days	Primary: Clinical response to treatment, overall and with regard to type of infection, at test-of-cure visit (i.e., cure, improvement, failure, missing, or indeterminate)	Primary: There was no difference in overall clinical cure rate; 81% with linezolid vs 71% with comparators (95% CI, -0.1 to 20.1). More patients with infected foot ulcers had a cure; 81% with linezolid vs 68% with comparators (P=0.018). Clinical cure rate in patients without osteomyelitis was 87% with linezolid and 72% with comparators (P=0.003). Adverse drug events were significantly more common in the linezolid group (27%) compared to the vancomycin group (10%; P=0.001). Adverse events occurring more frequently with linezolid therapy included nausea, anemia, and thrombocytopenia.
Stevens et al.[62] (2000) Linezolid 600 mg IV/PO every 12	MC, DB, DD, RCT Hospitalized patients ≥18 years of age with a	N=819 10-21 days	Primary: Clinical outcome and microbiological outcome based on	Primary: Of clinically evaluable patients (N=600), clinical cure rate was 88.6% in the linezolid group compared to 85.8% in the oxacillin/dicloxacillin group (P=0.300).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours vs oxacillin 2 g IV plus dicloxacillin 500 mg PO every 6 hours	suspected gram-positive complicated skin and soft tissue infection		resolution or improvement of clinical signs/symptoms of skin and soft tissue infections at the end of treatment compared with baseline	Of microbiologically evaluable patients (N=294), the cure rate was 88.1% in the linezolid group compared to 86.1% in the oxacillin/dicloxacillin group (P=0.606). No statistically significant differences were noted in the frequency of adverse events between treatment groups.
Yogev et al.[57] (2003) Linezolid 10 mg/kg IV/PO every 8 hours vs vancomycin 10 to 15 mg/kg IV every 6 to 24 hours (based on age) After 3 days of treatment, linezolid group was permitted to switch to PO linezolid, and vancomycin group was permitted to switch to a PO appropriate agent based on susceptibility tests.	RCT Hospitalized children <12 years of age with complicated skin and skin structure infections caused by resistant gram-positive bacteria	N=120 10-28 days	Primary: Patient clinical outcome and pathogen eradication rates	Primary: Clinical cure rate was 93.2% with linezolid vs 90% with vancomycin (P=0.594). Patients with a diagnosis of skin abscess had a significantly higher cure rate in the linezolid group compared to vancomycin (100% vs 60%, respectively; P=0.005). Patients with cellulitis or other types of infection had similar cure rates (P=NS for all). There was no statistically significant difference in eradication rates between treatment groups for all types of infections (P=NS for all). Fewer patients experienced adverse events with linezolid therapy compared to vancomycin (23% vs 48%, respectively; P=0.006). Vancomycin-treated patients experienced a greater incidence (statistically significant) of red man syndrome, pruritus, and rash. All other adverse events were not significantly different between treatment groups. The authors did not indicate the rate at which vancomycin was being infused.
Li et al.[58] (2003)	OL, MC, RCT	N=144	Primary: Length of hospital	Primary: In the clinically evaluable population, the unadjusted mean LOS was 5.3

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Linezolid 600 mg IV/PO BID vs vancomycin 1 g IV BID	Patients with complicated skin and soft tissue infections as the primary site of MRSA infection	Treatment: ≤4 weeks Observation: ≤4 weeks	stay (LOS)	days shorter with linezolid vs vancomycin (15.7 vs 21 days, respectively; P=0.0025). After adjusting for baseline variables, the between-treatment difference in mean LOS increased to 6.5 days with linezolid vs vancomycin (14.3 vs 20.8 days, respectively; P<0.001). Mean duration of IV therapy was shorter in the linezolid group (5.8 vs 12.6 days; P<0.0001). Clinically evaluable patients had to be treated for ≥7 days, which may have extended the LOS for patients receiving vancomycin IV as compared to the linezolid group that had the option to switch to PO therapy.
Itani et al.[59] (2005) Linezolid 600 mg IV/PO every 12 hours vs vancomycin 1 g IV every 12 hours	OL, MC, RCT Hospitalized patients with complicated skin and soft tissue infections due to MRSA	N=1,200 7 days	Primary: Length of stay, duration of IV treatment, and hospital discharge rates	Primary: Linezolid was associated with a shorter length of stay (P<0.01), decreased duration of IV antibiotic therapy (P<0.0001), and higher rates of hospital discharge (P<0.05) as compared to vancomycin therapy.
Itani et al.[129] (2010) Linezolid 600 mg IV/PO every 12 hours for 7 to 14 days vs vancomycin 15 mg/kg mg IV every 12 hours for 7 to 14 days	RCT, OL Patients ≥18 years of age with complicated skin and soft-tissue infections due to MRSA	N=1,077 7 to 10 days posttreatment	Primary: Clinical response, microbiologic outcome, length of stay, duration of IV therapy, safety	Primary: In the per protocol population, clinical success was reported in 92% of patients receiving linezolid compared to 88% of patients receiving vancomycin at the end of treatment (P=0.168). At the end of the study, clinical success rates were similar among the treatment groups (84% with linezolid and 80% with vancomycin; P=0.249). In the modified ITT population, clinical success was reported in 89% of patients receiving linezolid compared to 85% of patients receiving vancomycin at the end of treatment (P=0.090). At the end of the study, clinical success rates were similar among the treatment groups (81% with linezolid and 74% with vancomycin; P=0.048). In the per protocol population at the end of treatment, linezolid achieved a significantly higher rate of microbiologic success than vancomycin (85.4%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				vs 68.8%, respectively; P<0.001). At the end of the study, linezolid was comparable with vancomycin (75.0% vs 68.4%, respectively; P=0.127). In the modified intent-to-treat population, linezolid had a numerically higher success rate than vancomycin (74% vs 66%; 95% CI, -0.1 to 15.2; P=0.055). In the per protocol population, the median and mean lengths of stay were 6.0 and 7.6 days, respectively, in the linezolid group, compared to 7.0 and 8.9 days, respectively, in the vancomycin group (P=0.022). The mean duration of intravenous therapy was significantly shorter in the linezolid group than in the vancomycin group (5.6 vs 10.4 days; P<0.001). In the modified ITT population, the median and mean lengths of stay were 5.0 and 7.7 days, respectively, in the linezolid group, as compared with 7.0 and 8.9 days, respectively, in the vancomycin group (P=0.016). The mean duration of intravenous therapy was significantly shorter in the linezolid group than in the vancomycin group (5.3 vs 9.8 days; P<0.001). The percentage of patients who experienced ≥1 adverse event was similar in both treatment groups (linezolid, 48%; vancomycin, 51%). Treatment-related adverse events occurred in 23% of patients in the linezolid arm and 22% of patients in the vancomycin arm. Treatment- related nephrotoxic adverse events occurred more often in the vancomycin group. There were 11 deaths in the linezolid group and 7 deaths in the vancomycin group.
Sharpe et al.[60] (2005) Linezolid 600 mg PO every 12 hours vs vancomycin 1 g IV every 12 hours All patients	OL, RCT Patients ≥18 years of age with MRSA-related complicated skin and soft-tissue infections of the lower extremities	N=60 Treatment: 7-21 days Tests of cure: 10 days posttreatment	Primary: Clinical cure, improvement, or failure; microbiological eradication, persistence, or recurrence; duration of hospitalization and drug treatment	Primary: Linezolid was associated with a greater incidence of cure (50% vs 20% for vancomycin) and improvement (47% vs 23% for vancomycin; P=0.015 for both comparisons). Microbiological outcomes were similar overall between treatment groups (P=0.052). Median length of therapy was 10 days for both treatment arms; of these, 7 days of treatment were administered on an outpatient basis for the linezolid group compared to 4 outpatient days of treatment with vancomycin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
received perioperative cefazolin.				
Wilcox et al.[90] (2009) Linezolid 600 mg IV every 12 hours for 7-28 days vs vancomycin 1 g IV every 12 hours for 7-28 days	OL, MC Adults >13 years of age who had a central venous, pulmonary artery, or arterial catheter in place for 13 days and suspected catheter-related infection (CRBSI)	N=739 6 to 8 weeks	Primary: Microbiologic outcome at test of cure Secondary: Clinical outcomes and safety	Primary: Microbiologic outcomes at TOC met non-inferiority criteria in the 2 primary analysis populations. In the subset with complicated skin and skin-structure infections (cSSSI), success occurred in 146 (89.6%) of 163 linezolid patients and in 134 (89.9%) of 149 control patients (95% CI, -7.1 to 6.4). In the subset with CRBSI, microbiologic success occurred in 82 (86.3%) of 95 linezolid recipients and in 67 (90.5%) of 74 control patients (95% CI, -13.8 to 5.4). Secondary: In the subset of patients with cSSSI, clinical success occurred in 123 (77.8%) of 158 linezolid recipients and in 113 (77.9%) of 145 control patients at test-of-cure. In the subset with CRBSI, success occurred in 70 (75.3%) of 93 linezolid recipients and in 59 (80.8%) of 73 control patients. Sensitivity analysis did not alter clinical outcomes in the subsets with cSSSI (linezolid group, 75.0%; control group, 74.8%) or CRBSI (linezolid group, 73.7%; control group, 79.7%). Adverse events, including those unrelated to treatment, occurred in 244 linezolid recipients (67.2%) and were similar between groups. Mortality rates were 10.4% for linezolid recipients (28 of 269 patients) and 10.1% for control subjects (26 of 257) in the modified intent-to-treat population through test of cure, and they were 21.5% for linezolid recipients (78 of 363) and 16.0% for the control group (58 of 363; 95% CI, -0.2 to 11.2) for all treated patients through post-study treatment day 84.
Nichols et al.[63] (1999)	RCT, MC, OL Patients ≥18 years	N=893 17 months	Primary: Clinical success as defined as cure or	Primary: Clinical success rates for quinupristin-dalfopristin and the comparator group were 68.2% and 70.7%, respectively, indicating no significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Quinupristin-dalfopristin 7.5 mg/kg every 12 hours vs oxacillin 2 g every 6 hours or vancomycin 1 g every 12 hours	of age with complicated gram-positive skin or skin structure infection that required hospitalization for at least 24 hours and requiring at least 3 days of parenteral antibiotic therapy		improvement Secondary: Bacteriological response, safety and tolerability	difference between the therapies. Secondary: By-pathogen bacteriological eradication rates for all pathogens were lower in the quinupristin-dalfopristin group (66.6%) than the comparator group (77.7%, P=0.004). This difference was due to lower eradication rates for methicillin-sensitive *S aureus* (64.3% for quinupristin-dalfopristin and 76.6% for the comparator). For other pathogens, eradication rates were comparable. In addition, eradication rates in the quinupristin-dalfopristin for polymicrobial infections were lower than the comparator group (63.3% and 83.1%, respectively), but comparable for monomicrobial infections (72.6% and 70.8%, respectively). By-patient bacteriological success rate was comparable between quinupristin-dalfopristin (65.8%) and comparator regimens (72.7%). Clinical outcomes of patients receiving quinupristin-dalfopristin and vancomycin were comparable (68.4% vs 63.2%, respectively). Patients taking quinupristin-dalfopristin experienced more nausea, vomiting and pain than patients on the comparator drug (P=0.002, P=0.007, P=0.001, respectively). The percentage of patients reporting an adverse venous event was higher in the quinupristin-dalfopristin treatment group (66.2%) than the comparator group (28.4%). Discontinuation of patients due to adverse venous events was greater in the quinupristin-dalfopristin group (12.0%) than in the comparator group (2.0%).
Loeffler et al.[84] (2002) Quinupristin-dalfopristin 7.5 mg/kg IV every 8 to 12 hours	RETRO Patients <18 years of age with signs and symptoms of serious invasive infection	N=127 2 to 73 days	Primary: Clinical responses (cure, improved, failure, or indeterminate), microbiologic response (eradication, presumed eradication, presumed	Primary: Overall favorable clinical response rate (either cure or improved) was 69% and similar across all age groups. The overall favorable microbiologic response rate (either eradicated or presumed eradicated) was 78%. A total of 8% of patients experienced treatment-related non-venous adverse events. Pain (2%) and maculopapular rash (2%) were the most frequently reported drug-related adverse events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			persistence, persistence, or indeterminate), adverse events	Five patients discontinued treatment due to adverse laboratory events (3 of the 5 were related to treatment: gamma-glutamyl transferase, total bilirubin, and eosinophils). Forty-six patients died due to reasons unrelated to quinupristin-dalfopristin toxicities.
Stryjewski et al.[124] (2005) Telavancin 7.5 mg/kg IV once daily vs standard therapy (nafcillin or oxacillin 2 g IV every 6 hours, cloxacillin 0.5 to 1 g IV every 6 hours, or vancomycin 1 g IV twice daily)	RCT, DB, AC Patients ≥18 years of age with complicated skin and soft-tissue infections caused by gram-positive organisms	N=167 7 to 14 days posttreatment	Primary: Clinical response, microbiological response, safety	Primary: The median duration of treatment was 7 days in both groups. At the test-of-cure visit (7-14 days after the last dose of study medication), cure rates were 79% with telavancin and 80% with standard therapy (P=0.53). At the test-of-cure visit, 7% of patients receiving telavancin failed treatment compared to 4% of patients in the standard therapy group (no P value reported). For patients with S. *aureus* infection at baseline, 80% of patients in the telavancin group were cured and 77% of patients in the standard therapy group were cured (P=0.80). For patients with MRSA infection at baseline, cure rates were 82% for the telavancin group and 69% for the standard therapy group (P=1.00). A similar percentage of patients in each group (5%) discontinued therapy due to adverse events. Fewer serious adverse events were reported in the telavancin group than were for the standard therapy group.
Stryjewski et al.[125] (2006) Telavancin 10 mg/kg IV once daily vs standard therapy	RCT, DB, AC Patients ≥18 years of age with complicated skin and soft-tissue infections caused by gram-positive organisms	N=195 7 to 14 days posttreatment	Primary: Clinical cure in the clinically evaluable population, microbiological response, safety	Primary: Overall, at the test-of-cure visit (7-14 days after the last dose of study medication), cure rates were 82% with telavancin and 85% with standard therapy (P=0.37). Overall, at the test-of-cure visit, 3% of patients receiving telavancin failed treatment compared to 6% of patients in the standard therapy group (no P value reported). In the clinically evaluable population at the TOC visit, 96% of patients in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(nafcillin or oxacillin 2 g IV every 6 hours, cloxacillin 0.5 to 1 g IV every 6 hours, or vancomycin 1 g IV twice daily)				the telavancin group and 94% of patients in the standard therapy group were cured (P=0.53). In the microbiologically evaluable population at the TOC visit, 97% of patients in the telavancin group and 93% of patients in the standard therapy group were cured (P=0.37). In the microbiologically evaluable patients with *S. aureus* at baseline, 96% of patients in the telavancin group and 90% of patients in the standard therapy group were cured (P=0.36). In the microbiologically evaluable patients with MRSA at baseline, 96% of patients in the telavancin group and 90% of patients in the standard therapy group were cured (P=0.42). Among the microbiologically evaluable population, baseline pathogens were considered eradicated at the end-of-therapy (EOT) in 89% of patients in the telavancin group and in 77% of patients in the standard-therapy group (P=0.09). At TOC, pathogen eradication was higher, although not significantly, in those patients receiving telavancin (94% vs 83%; P=0.06). In patients with *S. aureus* at baseline, eradication at TOC was obtained in 92% of the patients receiving telavancin and 78% of the patients receiving standard therapy (P=0.07). In patients infected with MRSA, eradication rates were significantly higher in the telavancin group (92% vs 68%; P=0.04). Adverse events (AEs) were reported in 56% and 57% of the patients receiving telavancin and standard therapy, respectively. Similar percentages of patients in both groups experienced severe AEs (6% and 4% for the telavancin and standard therapy groups, respectively).
Stryjewski et al.[126] (2008) Telavancin 10 mg/kg IV once daily for 7 to 14 days	RCT, DB, AC (2 trials) Patients ≥18 years of age with complicated skin and soft-tissue	N=1,867 7 to 14 days posttreatment	Primary: Clinical response at the test-of-cure (TOC) visit (7 to 14 days after the last dose of study medication),	Primary: In all treated patients at the test-of-cure visit (study 0017), cure rates were 75.8% with telavancin and 74.8% with vancomycin (95% CI, -4.8 to 6.8). In study 0018, cure rates were 77.1% with telavancin and 73.7% with vancomycin (95% CI, -1.9 to 8.7). In the clinically evaluable population at the test-of-cure visit (study 0017),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs vancomycin 1 g IV twice daily for 7 to 14 days	infections caused by gram-positive organisms		microbiological response, safety	cure rates were 87.9% with telavancin and 86.5% with vancomycin (95% CI, -3.6 to 6.3). In study 0018, cure rates were 88.7% with telavancin and 87.6% with vancomycin (95% CI, -3.4 to 5.6). In the pooled analysis of all treated patients (study 0017 and 0018), cure rates were 76.5% with telavancin and 74.2% with vancomycin (95% CI, -1.6 to 6.2). In the clinically evaluable population (pooled analysis), cure rates were 88.3% with telavancin and 87.1% with vancomycin (95% CI, -2.1 to 4.6). Among the microbiologically evaluable patients, baseline pathogens were eradicated at the TOC visit in 89.8% and 87.3% of patients who received telavancin and vancomycin, respectively (95% CI, -1.4 to 6.2). Among patients with MRSA infection at baseline, cure rates were 91% with telavancin and 86% with vancomycin (95% CI, -1.1 to 9.3). Microbiologic eradication in patients with MRSA was 90% in the telavancin group and 85% in the vancomycin group (95% CI, -0.9 to 9.8). Overall therapeutic response was also evaluated. Patients were cured and pathogens were eradicated at the TOC visit in 88.6% and 86.2% of patients in the telavancin and vancomycin treatment groups, respectively (95% CI, -1.6 to 6.4). Adverse events were reported in 79% and 72% of patients who received telavancin and vancomycin, respectively. The incidence of serious adverse events was higher in the telavancin treatment group than in the vancomycin treatment group (7% vs 4%). More patients discontinued telavancin therapy than discontinued vancomycin therapy because of an adverse event (8% vs 6%). Except for taste disturbance, mild nausea, vomiting, and foamy urine in the telavancin group, adverse events were of similar type and severity between the treatment groups.
Corey et al.[111] (2010) Vancomycin 1 g plus aztreonam 1 g	RCT, MC, DB, AC Patients ≥18 years of age with complicated skin	N=702 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (8–15 days after administration	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the CE (91.1% vs 93.3%; 95% CI, 26.6 to 2.1) and MITT (86.6% vs 85.6%; 95% CI, 24.2 to 6.2) populations, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	and skin structure infections (cSSSIs) who required ≥5 days of parenteral antibacterial therapy		of the last dose of study medication) in the clinically evaluable (CE) and modified intent-to-treat (MITT) populations Secondary: Microbiological success rate, safety	Secondary: The clinical cure rate for MRSA cSSSIs was 95.1% for ceftaroline and 95.2% for vancomycin plus aztreonam. Similar cure rates were found in patients with MSSA (91.3% and 94.6%), as well as in the patients from whom Gram-negative pathogens were isolated. The microbiological success rate was similar for ceftaroline and vancomycin overall, and for MRSA. Among the ME patients, the baseline pathogen(s) was eradicated or presumed eradicated at similar rates in both the ME and mMITT populations (91.8% and 86.3% for ceftaroline; 92.5% and 83.7% for vancomycin plus aztreonam; difference, 20.7% and 2.7% [95% CI, 25.7 to 4.4 and 95% CI, 23.4 to 8.9], respectively). The incidence of AEs was similar in both study groups. The majority of AEs were mild in severity and similar in type among study groups. Diarrhea occurred in 3.4% vs 3.2% of patients in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively.
Wilcox et al.[112] (2010) Vancomycin 1 g plus aztreonam 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	RCT, MC, DB, AC Patients ≥18 years of age with complicated skin and skin structure infections (cSSSIs) who required ≥5 days of parenteral antibacterial therapy	N=694 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (8–15 days after administration of the last dose of study medication) in the clinically evaluable (CE) and modified intent-to-treat (MITT) populations Secondary: Microbiological success rate, safety	Primary: Cure rates at TOC were comparable in both treatment groups across all study populations. In the CE population, cure rates were 92.2% and 92.1% for ceftaroline and vancomycin plus aztreonam, respectively (95% CI, 24.4 to 4.5). In the MITT population, clinical cure rates for ceftaroline and vancomycin plus aztreonam were similar (85.1% vs 85.5%, respectively; 95% CI, 25.8 to 5.0). Secondary: In patients with MRSA isolated at baseline, cure rates were 91.4% and 93.3% for ceftaroline and vancomycin plus aztreonam, respectively. Similar cure rates were found in patients with MSSA (94.4% in both groups) as well as in the patients from whom a Gram-negative pathogen was isolated. Baseline pathogens were eradicated or presumed eradicated at similar rates in both the ME and mMITT populations among Gram-positive and a limited number of Gram-negative pathogens (92.9% and 86.6% for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				ceftaroline; 95.0% and 88.4% for vancomycin plus aztreonam; 95% CI, 26.9 to 2.5 and 95% CI, 27.5 to 3.9, respectively). There were no microbiological reinfections or recurrences at the LFU visit in either treatment group. The incidence of AEs was similar in both study groups. The majority of AEs were mild in severity and similar in type among study groups. Diarrhea occurred in 6.5% vs 4.4% in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively. AEs considered related to the study drug and occurring in ≥3% of patients were diarrhea and pruritus.
Corey et al.[113] (2010) Vancomycin 1 g plus aztreonam 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	Pooled analysis (2 trials) Patients ≥18 years of age with complicated skin and skin structure infections (cSSSIs) who required ≥5 days of parenteral antibacterial therapy	N=1,378 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (8–15 days after administration of the last dose of study medication) in the clinically evaluable (CE) and modified intent-to-treat (MITT) populations Secondary: Microbiological success rate, safety	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the CE (91.6% vs 92.7%) and MITT (85.9% vs 85.5%) populations, respectively. Secondary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in patients infected with MRSA (93.4% vs 94.3%). The efficacy of ceftaroline and vancomycin plus aztreonam against polymicrobial and monomicrobial infections was similar. Clinical relapse at the late follow-up visit was noted in 1.1% of patients in the ceftaroline group compared with 0.9% of patients in the vancomycin plus aztreonam group (CE). Favorable microbiological response (ME) was observed in 92.3% of patients in the ceftaroline group compared to 93.7% of patients in the vancomycin plus aztreonam group (95% CI, -4.8% to 2.0%). Incidences of treatment-emergent AEs were similar among the treatment groups. Diarrhea occurred in 4.9% of patients in the ceftaroline group and in 3.8% of patients in the vancomycin plus aztreonam group (MITT population). AEs considered to be related to study drug in ≥3% of patients were pruritus, nausea, and diarrhea.
Chuang et al.[117]	DB, RCT, MC	N=127	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) Vancomycin 1 g IV plus aztreonam 2 g IV every 12 hours vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours (TGC)	Hospitalized patients ≥18 years of age with complicated skin and skin structure infections (cSSSIs)	5 to 14 days	Clinical response in clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) populations Secondary: Clinical response (cure or failure) by baseline isolate and type of infection	In India, the clinical response rates in the CE and c-mITT populations were higher in the TGC group than in the vancomycin-aztreonam group. CE rates were 83.3% in patients treated with TGC and 75.8% in patients treated with vancomycin-aztreonam. The c-mITT cure rates for TGC vs vancomycin-aztreonam were 78.6% vs 66.7%, respectively. Small sample size prevented non-inferiority analysis. In Taiwan, the clinical response rates in the CE populations were lower in the TGC group than in the vancomycin-aztreonam group. CE rates were 78.6% in patients treated with TGC and 90.0% in patients treated with vancomycin-aztreonam. The c-mITT cure rates for TGC vs vancomycin-aztreonam were 73.3% and 75%, respectively. Small sample size prevented any meaningful statistical analysis. Secondary: In India, the number of isolates was small and no definitive inferences are possible. However, TGC demonstrated antimicrobial efficacy against isolates commonly linked to cSSSIs, including *E. Faecalis, E. Coli, S. aureus and S. agalactiae*. No MRSA isolates were noted among Indian patients. In Taiwan, few isolates were available. They included one patient with MRSA, which responded to TGC.
Gastrointestinal Infections				
Kearney et al.[76] (2000) Bismuth subsalicylate 2 tablets QID, tetracycline 500 mg QID, metronidazole 250 mg QID, and cimetidine 400 mg BID or famotidine 20 mg BID for 14	OL Patients with peptic ulcer disease or prescribed H_2-receptor antagonists or PPIs, and who tested positive with histology, rapid urease or urea breath testing for *H pylori* infection	N=224 6 weeks	Primary: Defining treatment success rates for *H pylori* infection at end of study Secondary: Adverse events	Primary: The intent-to-treat cure rates for BMT-H_2, BMT-PPI, and MLC were 81%, 87%, and 90%, respectively (all, P>0.05). The per-protocol cure rates for BMT-H_2, BMT-PPI, and MLC were 84%, 91%, and 92% (all, P>0.05). Secondary: The side-effect profile for the 3 treatment groups revealed no significant differences in the frequency of the most common side effects, diarrhea and constipation. Metallic taste was significantly more severe in the MLC group (P=0.04). Nausea was significantly more common in the MLC group than the BMT-H_2 group (P=0.04). There were no significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days (BMT-H_2) vs bismuth subsalicylate 2 tablets QID, tetracycline 500 mg QID, metronidazole 250 mg QID, and lansoprazole 30 mg BID for 7 days (BMT-PPI) vs metronidazole 500 mg BID, lansoprazole 30 mg BID, and clarithromycin 250 mg BID for 7 days (MLC)				differences in the frequency of dizziness/lightheadedness, cramping, or other side effects between the BMT-H_2 and MLC groups, and between BMT-PPI and BMT-H_2 groups. Severe headaches were significantly more frequent in the BMT-PPI group than the BMT-H_2 group (P=0.02). A significantly higher number of patients discontinued therapy due to adverse events in the BMT-H_2 and BMT-PPI treatment groups than the MLC group (P=0.049).
Magaret et al.[71] (2001) Bismuth subsalicylate 2 tablets QID, lansoprazole 30 mg BID, metronidazole 250 mg QID, and tetracycline 250 mg QID for 14 days	RCT, MC Patients years of age failing prior treatment for *H pylori*	N=48 6 weeks	Primary: Negative ^{14}C-UBT of <50 dpm at time of follow-up indicating cure of infection Secondary: Side effects and compliance	Primary: Per-protocol eradication rates for patients on triple therapy and quadruple therapy were 82% and 80%, respectively (P=0.85). Intention-to-treat eradication rates for triple and quadruple therapy were 72% and 65%, respectively (P=0.63). Secondary: Compliance in patients receiving triple and quadruple therapy was 89% (P=0.98). Side effects were reported in 84% of patients on triple therapy and 82% of patients on quadruple therapy (P=0.85). Side effects included nausea

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days				(33%), upset stomach (25%), diarrhea (36%), abdominal pain (16%), lightheadedness/dizziness (4%), and fatigue (8%).
Saad et al.[77] (2006) Bismuth-based quadruple therapies vs levofloxacin-based triple therapies	MA Patients infected with *H pylori*	N=854 (11 trials) 8 weeks	Primary: Eradication rates, incidence of adverse events, and incidence of discontinuation due to adverse events Secondary: Eradication rates of 7-day therapy vs 10-day therapy, eradication rates with levofloxacin 250 mg BID vs 500 mg BID	Primary: The results of 4 trials comparing levofloxacin-based triple therapy to bismuth-based quadruple therapy revealed eradication rates of 87% and 60%, respectively. Three of the 4 studies reported adverse-event frequency for levofloxacin-based therapy and bismuth-based therapy as 18.1% and 32.5%, respectively. Four trials demonstrated that adverse events were less likely to cause discontinuation of therapy with 10-day levofloxacin-based therapy than bismuth-based therapy. Secondary: Eleven trials compared the results of 7 days of levofloxacin-based therapy with those of 10 days of therapy. The corresponding eradication rates were 68% and 87%, respectively. Eight trials comparing efficacy of levofloxacin 250 mg BID to 500 mg BID revealed no significant difference in the eradication rates, which were 84% and 81%, respectively.
Miehlk et al.[72] (2003) Bismuth citrate 107 mg QID, omeprazole 20 mg BID,	RCT, XO Patients 18 to 80 years of age with at least one previous failure *of H pylori* therapy documented	N=84 26 months	Primary: Two negative biopsy-based tests, histology and rapid urease test, or a validated ^{13}C-urea breath test to	Primary: In the per-protocol analysis, patients on high-dose dual therapy and quadruple therapy achieved *H pylori* cure rates of 83.8% and 92.1%, respectively (P=0.71). Cure rates using intent-to-treat analysis were 75.6% and 81.4% for high-dose dual therapy and quadruple therapy, respectively, and were not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metronidazole 500 mg QID, and tetracycline 500 mg QID for 14 days vs omeprazole 40 mg QID and amoxicillin 750 mg QID for 14 days	by confirmatory examinations and antimicrobial resistance to both metronidazole and clarithromycin		confirm successful treatment	significantly different (P=0.60).
Perri et al.[78] (2001) Bismuth citrate 240 mg BID, pantoprazole 40 mg BID, metronidazole 250 mg TID, and tetracycline 500 mg QID for 10 days (quadruple therapy group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 150 mg every other day for 10 days (RIF 150 mg group)	PRO, RCT, OL Patients with *H pylori* infection confirmed by ^{13}C-urea breath test after failure of one or more standard regimens	N=135 6 weeks	Primary: Eradication rates as defined by negative ^{13}C-urea breath test 4 weeks after end of treatment Secondary: Side effect rates reported after end of treatment	Primary: By intent-to-treat analysis, eradication rates for the pantoprazole, amoxicillin and rifabutin 150 mg treatment group (RIF 150 mg group) were 66.6%. Eradication rates for pantoprazole, metronidazole, bismuth citrate, and tetracycline (quadruple therapy group) were also 66.6%. The eradication rate for pantoprazole, amoxicillin, and rifabutin 300 mg (RIF 300 mg group) was 86.6%, which was significantly different than the other two treatment groups (P<0.025). Secondary: There was a significant difference in the side effects observed in rifabutin-treated patients compared to patients receiving quadruple therapy. The rates of side effects were 9%, 11% and 47%, (P<0.0001), for the triple therapies with the RIF 150 mg group, RIF 300 mg group, and quadruple therapy group, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 300 mg every other day for 10 days (RIF 300 mg group)				
Katelaris et al.[75] (2002) Bismuth subcitrate 108 mg QID, pantoprazole 40 mg BID, tetracycline 500 mg QID, metronidazole 200 mg TID and 400 mg PM for 7 days (PBTM7) vs bismuth subcitrate 108 mg QID, tetracycline 500 mg QID, and metronidazole 200 mg TID and 400 mg PM for 14 days (BTM14) vs	RCT, MC, OL, PG Patients ≥18 years of age with *H pylori* infection confirmed by a positive urease test and confirmatory histology and ^{13}C-urea breath test	N=405 8 weeks	Primary: At week 8, ^{13}C-urea breath test to determine the outcome of eradication therapy Secondary: Compliance and adverse event profile	Primary: By intent-to-treat analysis, the eradication rates for the PAC7, PBTM7, and BTM14 treatment groups were 78%, 82% and 69%, respectively. By per-protocol analysis, the corresponding eradication rates were 82%, 88%, and 74%, respectively. In both analysis, the eradication rates for PBTM7 and PAC7 were not significantly different (all P>0.05), while eradication rates for PBTM7 were significantly higher than BTM14 (P=0.01). Secondary: Adverse effects were common in all treatment groups. Adverse effects that interfered with activities of daily living were significantly higher in the BTM14 group (P<0.01). The number of patients who discontinued treatment due to adverse effects was also higher in the BTM14 group (9%) vs the PBTM7 group (3%) and the PAC7 group (2%). Noncompliance, defined as less than 90% of study drug taken, was higher in BTM14 than PBTM7 and PAC7.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pantoprazole 40 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg BID (PAC7)				
Uygun et al.[85] (2007) Bismuth subsalicylate 300 mg QID, lansoprazole 30 mg BID, tetracycline 500 mg QID, and metronidazole 500 mg TID (BLTM group) vs lansoprazole 30 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID (LAC)	RCT, SC, SB Patients with *H. pylori* infection and non-ulcer dyspepsia	N=240 14 days	Primary: *H. pylori* eradication rates	Primary: The ITT and PP populations, *H. pylori* eradication rates were 70% (95% CI, 61–78) and 82.3% (95% CI, 74–89) in the BLTM group, and 57.5% (95%CI 48–66) and 62.7% (95%CI 53–71) in the LAC group. The BLTM treatment achieved a significantly better eradication rate than the LAC treatment in PP analysis (82.3% vs 62.7%, P=0.002). Although a better ITT rate was obtained in the BLTM group than in the LAC group, the difference was not significant (70% vs 57.5%, P=0.06). Mild to severe side-effects, which were more frequent in the BLTM group, were reported in 18.2% of the patients. Although it was not statistically significant, the number of patients ceasing the treatment for side-effects was more in BLTM group than in the LAC group.
Wu et al.[122] (2011) Bismuth subcitrate 120 mg QID, esomeprazole 40 mg BID, tetracycline 500 mg QID, and metronidazole for	RCT Patients ≥18 years of age with persistent *H. pylori* infection who failed standard first-line therapy (proton-pump inhibitor, clarithromycin and	N=120 8 weeks posttreatment	Primary: Eradication rates, adverse events, resistance rates, compliance	Primary: In the ITT analysis, there was a significantly lower eradication rate for the EBTA group (62%; 95% CI, 50% to 75%) than for the EBTM group (81%; 95% CI, 71% to 91%; P=0.02). In the PP analysis, *H. pylori* infection was eradicated in 64% of the EBTA group (95% CI, 52% to 76%) and 83% of the EBTM group (95% CI, 74% to 92%; P=0.01). A total of 19% of patients in the EBTA group and 44% of patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
7 days as rescue therapy (EBTM) vs bismuth subcitrate120 mg QID, esomeprazole 40 mg BID, tetracycline 500 mg QID, and amoxicillin 500 mg QID for 7 days as rescue therapy (EBTA)	amoxicillin)			EBTM group reported at least 1 adverse event during eradication therapy. The EBTA group had fewer adverse events than the EBTM group (P=0.004). The frequency of nausea in the EBTA group was lower than in the EBTM group (5% vs 16%, respectively). Tetracycline- and metronidazole-resistant strains were found in 2% and 53% of the patients, respectively. No strains developed resistance to amoxicillin. In the EBTA group, the *H. pylori* eradication rate for the tetracycline-susceptible strains was 67% by ITT analysis and 68% by PP analysis. All the strains in the subgroup were susceptible to amoxicillin. In the EBTM group, no tetracycline-resistant strains existed. The eradication rate of tetracycline-susceptible strains was 80% and 83% by ITT and PP analyses, respectively. With respect to metronidazole resistance, eradication rates were similar between susceptible and resistant strains by either ITT or PP analyses. Compliance rates were 97% in both treatment groups (P=1.00).
Songür et al.[123] (2009) Bismuth subcitrate 300 mg QID, lansoprazole 30 mg BID, tetracycline 500 mg QID, and metronidazole 500 mg BID for 10 days (BLTM) vs ranitidine bismuth citrate 400 mg BID, lansoprazole 30 mg BID, tetracycline 500 mg QID, and	RCT, SC Patients with *H. pylori* infection and dyspeptic symptoms	N=464 14 days	Primary: Eradication rates, compliance	Primary: In the per protocol analysis, eradication rates in LAC, BLTM, RBLTM, and LTM groups were 35.6%, 54.9%, 64.4%, and 60%, respectively. In the ITT analysis, eradication r rates in LAC, BLTM, RBLTM, and LTM groups were 32.7%, 47.1%, 57.3%, and 54.8%, respectively. The BLTM, RBLTM, and LTM treatment groups achieved a significantly better eradication rate than the LAC treatment group (P<0.001). There was no significant difference between BLTM, RBLTM, and LTM treatment groups. Compliance rates with LAC, BLTM, RBLTM, and LTM therapies were 91%, 87%, 90%, and 94%, respectively. The treatments were generally well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metronidazole 500 mg BID for 10 days (RBLTM) vs lansoprazole 30 mg BID, tetracycline 500 mg QID, and metronidazole 500 mg BID for 10 days (LTM) vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days (LAC)				
Malfertheiner et al.[121] (2011) Bismuth subcitrate potassium 140 mg, metronidazole 125 mg, and tetracycline 125 mg (as a single three-in-one capsule) 3 capsules QID plus omeprazole 20 mg BID for 10 days (quadruple	RCT, OL Patients ≥18 years of age with *H. pylori* infection and upper gastrointestinal symptoms	N=399 56 days posttreatment	Primary: Eradication rates, resistance rates, and safety	Primary: In the per protocol analysis, eradication rates were 93% with quadruple therapy compared to 70% with standard therapy (P<0.0001). Quadruple therapy was found to be non-inferior to standard therapy. In the intention-to-treat analysis, eradication rates were 80% with quadruple therapy compared to 55% with standard therapy (P<0.0001). Metronidazole sensitivity did not significantly affect the efficacy of quadruple therapy in the per protocol population (P=0.283). Clarithromycin sensitivity seemed to significantly affect the efficacy of standard therapy (P<0.0001). Simultaneous metronidazole and clarithromycin resistance reduced efficacy only in patients treated with standard therapy (P=0.001). The incidence of serious TEAEs and discontinuations due to a TEAE were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy) vs omeprazole 20 mg, amoxicillin 500 mg, and clarithromycin 500 mg BID for 7 days (standard therapy)				similar between groups (<2.0%). The main adverse events were gastrointestinal and CNS disorders.
Zheng et al.[119] (2010) Colloidal bismuth subcitrate 220 mg BID, pantoprazole 40 mg BID, metronidazole 400 mg TID, and tetracycline 750 mg BID for 10 days (PBMT) vs pantoprazole 40 mg BID, amoxicillin 1.0 g BID and clarithromycin 500 mg BID for 7 days (PAC)	RCT, SC, OL Patients 18 to 70 years of age with non-ulcer dyspepsia (NUD) and *H. pylori* infection	N=170 7 to 10 days	Primary: Eradication rates, resistance rates, safety	Primary: In the ITT analysis, eradication rates were 63.5% in the PAC group and 89.4% in the PBMT groups (P<0.05). In the per protocol analysis, the eradication rates were 65.1% in the PAC group and 91.6% in the PBMT group (P<0.05). The *H. pylori* primary resistance rates to metronidazole and clarithromycin were 41.6% and 20.8%, respectively, whereas all the *H. pylori* isolates were sensitive to amoxicillin and tetracycline. Adverse events were similar among the treatment groups and included bitter taste, nausea, poor appetite, and occasional symptoms, such as diarrhea, vomiting, drug eruption, insomnia, constipation, and lethargy. The adverse events rates of quadruple therapy and triple therapy were 42.3 and 60.0%, respectively.
de Boer et al.[79] (1998) Ranitidine bismuth citrate 400 mg	OL, RCT, PG Patients with upper gastrointestinal symptoms and	N=168 8 weeks	Primary: Endoscopy performed six weeks after completion of	Primary: Logistical regression analysis determined that there was no difference between the 7-day and 14-day treatments. Intent-to-treat analysis cure rate for the ranitidine bismuth citrate, tetracycline, and metronidazole treatment group was 86%. The cure rate for the ranitidine bismuth citrate,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID, tetracycline 500 mg QID, metronidazole 500 mg TID for 7 days vs ranitidine bismuth citrate 400 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 7 days vs ranitidine bismuth citrate 400 mg BID, clarithromycin 500 mg BID for 14 days	infected with *H pylori*		treatment to determine *H pylori* infection, defined as a positive CLOtest, confirmed by histology or culture Secondary: Safety	amoxicillin, and clarithromycin treatment group was 92%. The cure rate for the ranitidine bismuth citrate and clarithromycin treatment group was 95%. Per-protocol cure rates were 89%, 93%, and 96% respectively. There was no statistical difference between the three groups. Secondary: Side effects were comparable among the treatment groups. Overall, 32% of patients in the ranitidine bismuth citrate, tetracycline, metronidazole treatment group, 18% of the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group, and 23% of the ranitidine bismuth citrate and clarithromycin treatment group reported side effects during the trial period (P=0.249).
Altintas et al.[73] (2004) Ranitidine-bismuth citrate 400 mg BID, tetracycline 1 g BID, and metronidazole 500 mg TID for 14 days (triple therapy) vs ranitidine-bismuth	RCT Patients ≥18 years of age who were resistant to triple therapy consisting of a PPI, clarithromycin and amoxicillin for the treatment of *H pylori*	N=52 6 weeks	Primary: Eradication rates of *H pylori* as confirmed by endoscopy and biopsy Secondary: Improvement in symptoms of endoscopic gastritis	Primary: There was a significant difference between the treatment groups. Eradication rates for triple and dual therapy were 44.4% and 12%, respectively (P=0.01). Secondary: There were significant improvements in the severity of endoscopic gastritis in both groups (P=0.01), but no significant differences between the two groups (P=0.600).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
citrate 1 g BID for 14 days and azithromycin 500 mg QD for 7 days (dual therapy)				
Laine et al.[74] (1997) Ranitidine bismuth citrate 400 mg BID, amoxicillin 1 g BID, and clarithromycin 500 mg BID vs ranitidine bismuth citrate 400 mg BID, metronidazole 500 mg TID, and tetracycline 500 mg TID	PRO, RCT Patients ≥18 years of age with previously untreated *H pylori* infection documented by ^{13}C-urea breath test and endoscopic biopsy or rapid quantitative serologic test	N=100 6 weeks	Primary: At completion of study, eradication rates based on ^{13}C-urea breath test Secondary: Compliance measured at end of study	Primary: Intent-to-treat analysis showed eradication rates for ranitidine bismuth citrate, amoxicillin, and clarithromycin therapy and ranitidine bismuth citrate, metronidazole and tetracycline therapy were 92% and 80%, respectively (per-protocol analysis showed eradication rates of 96% and 88%, respectively). Secondary: Three patients in the ranitidine bismuth citrate, amoxicillin, and clarithromycin group were not compliant due to side effects of the treatment. Six patients taking ranitidine bismuth citrate, metronidazole and tetracycline therapy were not compliant due to side effects of the treatment.
Luther et al.[120] (2010) Bismuth quadruple therapy (metronidazole, bismuth-containing compound, tetracycline, and proton-pump inhibitor) vs	MA Patients with *H. pylori* infection	N=1,679 (9 trials) Variable duration	Primary: Eradication rate, compliance rate, adverse events	Primary: The eradication rate with bismuth quadruple therapy was 78.3% compared to 77% with clarithromycin triple therapy (RR, 1.002, 95% CI, 0.936 to 1.073). The compliance rate with bismuth quadruple therapy was 92.6% compared to 98.9% with clarithromycin triple therapy (RR, 0.99; 95% CI, 0.938 to 1.045). The overall incidence of adverse events in patients receiving bismuth quadruple therapy was 35.5% compared to 35.4% with clarithromycin triple therapy (RR, 1.037; 95% CI, 1.037 to 1.135).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clarithromycin triple therapy (amoxicillin, clarithromycin, and proton-pump inhibitor)				
Musher et al.[130] (2009) Nitazoxanide 500 mg every 12 hours for 10 days vs vancomycin 125 mg every 6 hours for 10 days	RCT, DB Patients with *Clostridium difficile* infection (CDI), ≥3 loose stools within 24 hours and ≥1 of the following additional findings: fever, abdominal pain, and/or leukocytosis	N=50 31 days	Primary: Clinical response at the end of treatment (resolution of all findings of CDI) Secondary: Time to resolution of symptoms and sustained response rate at day 31 (end-of treatment response with no recurrence)	Primary: A response to treatment was documented in 74% of vancomycin-treated patients and 77% of nitazoxanide-treated patients (95% CI, –24 to 28). Among those who completed therapy, rates of response were 87% for those who received vancomycin and 94% for those who received nitazoxanide (95% CI, -18 to 30). Secondary: The time to complete resolution of all symptoms of CDI was similar in the two groups (P=0.55). After an initial response, 2 vancomycin patients and 1 nitazoxanide patient experienced relapse within 31 days after the start of treatment. In the ITT analysis, sustained response rates were 67% for vancomycin-treated patients and 73% for nitazoxanide-treated patients (95% CI, -22 to 32). In the completers analysis, sustained response rates were 78% for vancomycin-treated patients and 89% for nitazoxanide-treated patients (95% CI, -18 to 35). Serious adverse events affected 15% of patients who received vancomycin and 9% of patients who received nitazoxanide. Five vancomycin-treated patients and no nitazoxanide-treated patients had new mild-to-moderate gastrointestinal symptoms during treatment.
Pimentel et al.[83] (2011) TARGET 1 TARGET 2	RCT, DB, PC (2 trials) Patients ≥18 years of age with irritable bowel syndrome	N=1,260 12 weeks	Primary: Proportion of patients who had adequate relief of global IBS symptoms (weeks	Primary: Significantly more patients in the rifaximin group than in the placebo group experienced adequate relief of global IBS symptoms during at least 2 of the first 4 weeks after treatment (40.8% vs 31.2%, P=0.01, in TARGET 1; 40.6% vs 32.2%, P=0.03, in TARGET 2; 40.7% vs 31.7%, P<0.001, in the two studies combined).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rifaximin 550 mg three times daily for 14 days vs placebo	(IBS) without constipation		3 through 6) Secondary: Proportion of patients who had adequate relief of IBS-related bloating, percentage of patients who had a response to treatment as assessed by daily self-ratings of global IBS symptoms and individual symptoms of bloating, abdominal pain, and stool consistency	The proportion of patients with a response to treatment was significantly greater in the rifaximin group than in the placebo group (42.7% vs 30.6%, P<0.001, in TARGET 1; 37.8% vs 28.4%, P=0.007, in TARGET 2; 40.2% vs 29.5%, P<0.001, in the two studies combined). Secondary: More patients in the rifaximin group than in the placebo group had adequate relief of bloating during at least 2 of the first 4 weeks after treatment (39.5% vs 28.7%, P=0.005, in TARGET 1; 41.0% vs 31.9%, P=0.02, in TARGET 2; 40.2% vs 30.3%, P<0.001, in the two studies combined). A significantly greater proportion of patients in the rifaximin group than in the placebo group had relief of IBS-related bloating (39.2% vs 32.5%, P=0.05, in TARGET 1; 43.5% vs 30.9%, P<0.001, in TARGET 2; 41.3% vs 31.7%, P<0.001, in the two studies combined). A significantly greater proportion of patients in the rifaximin group than in the placebo group had relief of IBS-related abdominal pain and discomfort during the primary evaluation period (44.3% vs 36.3%, P=0.03, in TARGET 1; 42.9% vs 34.4%, P=0.02, in TARGET 2). In an assessment of the composite end point of abdominal pain or discomfort and loose or watery stools, significantly more patients in the rifaximin group than in the placebo group had relief during the primary evaluation period (46.6% vs 38.5%, P=0.04, in TARGET 1; 46.7% vs 36.3%, P=0.008, in TARGET 2), and a significantly greater proportion of patients in the rifaximin group had relief with respect to the individual components of this end point. More patients in the rifaximin group than in the placebo group in both studies had adequate relief of global IBS symptoms within the first month, with continued relief during the first 2 months and during all 3 months in both studies (P=0.05 in TARGET 1, P=0.005 in TARGET 2, and P<0.001 in the two studies combined, for relief during all 3 months).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients treated with rifaximin had adequate relief of global IBS symptoms during the entire 3 months of the study compared to placebo (P=0.003 in TARGET 1, P=0.01 in TARGET 2, and P<0.001 in the two studies combined) and of IBS-related bloating compared to placebo (P=0.01 in TARGET 1, P<0.001 in TARGET 2, and P<0.001 in the two studies combined). The incidence of adverse events was similar in the two groups.
Steffen et al.[64] (2003) Rifaximin 600 mg TID vs rifaximin 1,200 mg TID vs placebo	MC, PG, DB, RCT Adult travelers affected by acute diarrhea with at least one sign of enteric infection	N=380 Treatment: 3 days Follow-up: 5 days	Primary: Time elapsed from ingestion of first dose to passage of the last unformed stool (TLUS); wellness (clinical cure) Secondary: Number of subjects with improvement of diarrhea during 24 hour intervals, number of unformed stools passed per time interval, number of subjects declared "well," treatment failures, and microbiological cure	Primary: Median time to last unformed stool was 32.5 and 32.9 hours for rifaximin 600 mg and 1,200 mg, respectively, compared to 60 hours for placebo (P=0.0001 for each treatment group vs placebo). Clinical cure within 120 hours was noted at a greater rate with rifaximin 600 mg and 1,200 mg (79.2% and 81%, respectively) compared to placebo (60.5%; P=0.001 for each treatment group vs placebo). Secondary: Improvement of diarrhea was greater in the rifaximin 600 mg group compared to placebo. In the 24-48 hour interval, improvement was seen in 87% of patients given rifaximin 600 mg and 72% in placebo-treated patients (P=0.007); in the 48-72 hour interval, improvement was seen in 91% of patients given rifaximin 600 mg and 78% in placebo-treated patients (P=0.008). Although the rate of improvement was greater than placebo overall, the differences did not reach statistical significance. Mean number of unformed stools passed was 3.1 for rifaximin groups vs 3.8 for placebo (day 1), 1.6 for rifaximin groups vs 2.6 for placebo (day 2), 0.5 for rifaximin groups vs 0.9 for placebo (final day; P=0.001, repeated measures analysis of variance). Treatment failures were noted 16%-16.7% of the time with both rifaximin groups vs 34.8% with placebo-treated patients (P=0.001). Rate of microbiological cure was not significantly different across treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most common adverse events were GI-related. Headache was also frequently reported, though with no difference between groups. Fatigue was reported more often with rifaximin 1,200 mg (1.1%, P=0.023).
Dupont et al.[97] (2005) Rifaximin 200 mg QD vs rifaximin 200 mg BID vs rifaximin 200 mg TID vs placebo	RCT, DB, PC Healthy students ≥18 years of age attending classes in Guadalajara, Mexico who ingested the study drug within 72 hours of arrival in Mexico	N=210 2 weeks	Primary: Occurrence of diarrhea Secondary: Occurrence of mild diarrhea (defined as passage of 1 to 2 unformed stools plus a symptom) and number of days of occurrences of moderate to severe enteric symptoms per 100 person-days of observation	Primary: Over the two week treatment period, diarrhea developed in 53.7% of patients in the placebo group, 12% of patients in the once-daily rifaximin group (RR, 0.22; 95% CI, 0.10-0.49), 19.23% of patients in the rifaximin twice daily group (RR, 0.36; 95% CI, 0.19-0.66), 12.96% of patients in the rifaximin three times daily group (RR, 0.24; 95% CI, 0.12-0.50), and 14.74% of the combined rifaximin groups (RR, 0.27; 95% CI, 0.17-0.43). Diarrhea was prevented in all of the rifaximin groups (P<0.001 for each rifaximin group vs placebo). The protection rates were 72% and 77% against travelers' diarrhea and antibiotic-treated diarrhea, respectively (P<0.001 for both). Secondary: Rifaximin reduced the occurrence of mild diarrhea compared to placebo (P=0.02). In those who did not develop diarrhea, rifaximin significantly reduced the occurrence of moderate and severe intestinal problems (P=0.009 for pain or cramps; P=0.02 for excessive gas) compared to placebo. The incidence of adverse events was comparable between the rifaximin groups and the placebo group.
Martinez-Sandoval et al.[98] (2010) Rifaximin 600 mg QD for 2 weeks vs placebo	RCT, DB, MC Healthy students ≥18 years of age attending classes in Guadalajara, Mexico who ingested the study drug within 72 hours of arrival in Mexico	N=210 2 weeks	Primary: Occurrence of travelers' diarrhea (TD) Secondary: Incidence of TD resulting from all causes; incidence of TD associated with diarrheagenic	Primary: Prophylactic treatment with rifaximin significantly reduced the risk of developing TD compared to placebo (15% vs 47%, respectively; P<0.0001). Secondary: A smaller percentage of patients who received rifaximin developed TD (20%) compared with those who received placebo (48%; P<0.0001). A smaller percentage of patients who developed TD in the rifaximin group received rescue therapy compared with placebo (14% vs 32%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			E coli; incidence of TD associated with invasive bacterial pathogens; incidence of TD occurring in the 7-day follow-up period; protection rates against TD, TD associated with diarrheagenic *E coli*, and TD associated with invasive bacterial pathogens; number of participants with symptoms of enteric infection and mild diarrhea without TD	respectively; P=0.003). There was no significant difference in the percentage of patients who developed TD associated with diarrheagenic *E coli* with rifaximin compared to placebo (9% vs 18%, respectively; P=0.098). TD was not associated with invasive bacterial pathogens in any patient. The percentage of individuals who developed TD associated with unidentified pathogens was significantly lower in the rifaximin vs placebo group (11% vs 30%, respectively; P=0.01). A greater percentage of patients who received rifaximin completed the 14-day treatment course without developing TD (76%) compared to those who received placebo (51%; P=0.0004). The percentage of patients who experienced mild diarrhea, but did not develop TD, was similar between the rifaximin and placebo groups (29% vs 21%, respectively). During the 7-day post-treatment period, the percentage of patients who developed TD was similar for rifaximin (16%) vs placebo (15%). The protection rates achieved with rifaximin prophylaxis were similar for TD (58%; 95% CI, 35–73) and TD requiring rescue antibiotic therapy (56%; 95% CI, 23–75).
DuPont et al.[66] (2001) Rifaximin 400 mg BID vs ciprofloxacin 500 mg BID	DB, RCT Students ≥18 years of age traveling to Mexico or Jamaica with diarrhea	N=187 3 days	Primary: Rapidity of resolution of diarrhea and modification of stools as measured by the time to last unformed stool (TLUS)	Primary: The median time to last stool was 25.7 hours (95% CI, 20.9 to 38) for the rifaximin group and 25 hours (95% CI, 18.5 to 35.2) for the ciprofloxacin group. Criteria for wellness, indicated by a TLUS of 0 hours, were noted for 8% (7/93) of patients given rifaximin compared to 20% (19/94) of patients given ciprofloxacin. Secondary: There was no significant difference between groups with respect to number of unformed stools passed (P=0.267). Improvement within 0-24 hours and 24-48 hours was similar between rifaximin and ciprofloxacin (P=0.419 and P=0.667 for each time interval).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No difference in failure to respond to treatment (P=0.411) or microbiological cure (P=0.222). Nausea was more common with ciprofloxacin at 24-48 hours (34% vs 18%; P=0.012) and at 48-72 hours (23% vs 10%; P=0.009). However, the incidence of tenesmus was more common in the rifaximin group at 0-24 hours (rate not provided; P=0.016) but not significantly so during the 24-48 or 48-72 hour intervals (P=0.348).
Taylor et al.[99] (2006) Rifaximin 200 mg TID vs ciprofloxacin 500 mg BID vs placebo Treatment was to begin ≤72 hours after the onset of diarrhea and was continued for 3 days.	RCT, DB, MC, PG Patients ≥18 years of age who consulted one of seven travel health clinics in Mexico, Guatemala, India, or Peru with acute diarrhea, fecal urgency, blood and/or mucus in the stool, or tenesmus	N=399 3 days	Primary: Time to last unformed stool (TLUS) Secondary: Proportion of patients with improvement in diarrheal syndrome, number of unformed stools passed per unit of time, the proportion of patients with wellness, and the proportion of patients who failed treatment	Primary: TLUS in the rifaximin group was 32.0 hours compared to 65.5 hours in the placebo group (P=0.0014; RR, 1.63; 95% CI, 1.21-2.19). TLUS in the ciprofloxacin group was 28.8 hours (P=0.0003; RR, 1.89; 95% CI, 1.34-2.65 vs placebo). There was no significant difference between rifaximin and ciprofloxacin (P=0.35; RR, 0.88; 95% CI, 0.66–1.15). Secondary: Rifaximin was more effective than placebo for secondary endpoints including improvement in diarrheal syndrome (P<0.05), number of unformed stools passed after the first dose of study medication (P=0.0002), proportion of patients achieving wellness (P=0.0039), and the incidence of treatment failure (P=0.0115). Ciprofloxacin was more effective than placebo on these endpoints as well (P<0.05). There was no significant difference between rifaximin and ciprofloxacin for improvement of diarrhea (P>0.05) and achievement of wellness (P=0.74). Ciprofloxacin was more effective than rifaximin for number of unformed stools passed (6.2 vs 8.8, respectively; P<0.0004) and incidence of treatment failure (P=0.05). The incidence of adverse events was similar among the treatment groups.
DuPont et al.[65] (1998) Rifaximin 200 mg TID vs	PRO, DB, RCT Students ≥18 years of age from the Unites States with acute diarrhea who were attending a university in	N=72 5 days	Primary: Duration of diarrhea (time to last unformed stool after which patient was declared well), and diarrhea improvement	Primary: Data from the present study was compared to data from 2 historical placebo-controlled trials. There were no significant differences between groups in mean durations of post-enrollment diarrhea. The shortest duration of diarrhea was seen with rifaximin 200 mg (36.9 hours) and the greatest with SMX-TMP (55.7 hours; P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rifaximin 400 mg TID vs rifaximin 600 mg TID vs SMX-TMP 160 mg/800 mg BID	Mexico			The incidence of improvement in diarrhea after 24 hours for rifaximin 200 mg, 400 mg, 600 mg, and SMX-TMP was 56%, 44%, 53%, and 65%, respectively. The corresponding rates of improvement in diarrhea after 48 hours were 83%, 78%, 89%, and 76%, respectively. Clinical failure occurred for 11% of overall rifaximin-treated patients compared to 29% treated with SMX-TMP (P=NS). Number of unformed stools passed during 5 days of treatment was lower with overall rifaximin-treated patients (5.9) compared to patients receiving placebo in 2 earlier published trials (11.4 and 9.8; P=NS). Mean duration of diarrhea was significantly lower in rifaximin-treated patients (43.1 hours) compared to placebo (68.1 hours and 81.9 hours; P=0.001 for both comparisons). At baseline, the mean length of diarrhea before treatment was greater in the SMX-TMP group (32.8 hours) vs all rifaximin groups (25.3-30 hours) and mean number of unformed stools were also greater with SMX-TMP (6.5) compared to the rifaximin groups (5.7-6.1).
DuPont et al.[94] (2007) Rifaximin 200 mg TID for 3 days vs loperamide 4 mg initially, followed by 2 mg after each unformed stool vs rifaximin 200 mg	RCT Adults with acute diarrhea (≥3 unformed stools in 24 hours) with ≥ 1 symptom of enteric infection	N=310 5 days	Primary: Median time from beginning therapy until passing the last unformed stool	Primary: Rifaximin and rifaximin-loperamide significantly reduced the median time until passage of the last unformed stool (32.5 hours and 27.3 hours, respectively) compared to loperamide (69 hours; P=0.0019). The mean number of unformed stools passed during illness was lower with rifaximin-loperamide (3.99) compared with rifaximin (6.23; P=0.004) or loperamide alone (6.72; P=0.002). All treatments were well tolerated with a low incidence of adverse events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
TID for 3 days plus loperamide 4 mg initially, followed by 2 mg after each unformed stool				
Louie et al.[110] (2011) Vancomycin 125 mg orally four times daily for 10 days vs fidaxomicin 200 mg twice daily for 10 days	MC, DB, RCT Patients ≥16 years of age with diarrhea and a diagnosis of *C. difficile* infection, as well as the presence of *C. difficile* toxin A, B, or both in the stool	N=629 28 days posttreatment	Primary: Clinical cure (resolution of symptoms and no need for further therapy for *C. difficile* infection as of the second day after the end of the course of therapy) Secondary: Recurrence of *C. difficile* infection (diarrhea and a positive result on a stool toxin test within 4 weeks after treatment)	Primary: Clinical cure rates in the modified ITT analysis were 88.2% with fidaxomicin and 85.8% with vancomycin. Clinical cure rates in the PP analysis were 92.1% for fidaxomicin and 89.8% for vancomycin. The rates of clinical cure with fidaxomicin were non-inferior to those with vancomycin. Secondary: Recurrence in the modified ITT analysis was 15.4% with fidaxomicin compared to 25.3% with vancomycin (P=0.005). Recurrence in the PP analysis was 13.3% with fidaxomicin compared to 24% with vancomycin (P=0.004). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection.
McFarland et al.[52] (2002) Vancomycin ≤1 g to ≥2 g PO per day; taper, pulse, or combination with another antimicrobial vs	DB, PC, RCT (2 trials) Patients age 18-91 years with recurrent episodes of *C difficile* disease (RCDD); ≥1 prior episode within 1 year	N=163 2-4 months	Primary: Incidence of another *C difficile* recurrence during study subsequent to the enrollment episode, or incidence of cure (i.e., absence of recurrence) 2 months after	Primary: *C difficile* was cleared in 89% of the vancomycin group vs 59% of the metronidazole group (P<0.001). Tapered and pulsed dose courses of vancomycin resulted in fewer recurrences than metronidazole (P=0.01 and P=0.02, respectively). Overall failure rates did not differ significantly (P=0.77).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metronidazole ≤1 g to 2 g PO per day; taper or pulse			antibiotic treatment	
Bricker et al.[53] (2005) Vancomycin PO vs metronidazole or bacitracin or fusidic acid* or teicoplanin* or rifaximin vs placebo	MA of RCTs Patients with diarrhea who recently received antibiotics for an infection other than *C difficile*	N=582 Variable duration	Primary: Initial resolution of diarrhea, initial conversion of stool to *C difficile* cytotoxin and/or stool culture negative, recurrence of diarrhea, recurrence of fecal *C difficile* cytotoxin and/or positive stool culture, patient response to cessation of prior antibiotic therapy Secondary: Rates of sepsis, emergent surgery, fecal diversion or colectomy, and death	Primary: For initial symptomatic resolution, metronidazole, bacitracin, teicoplanin, fusidic acid, and rifaximin were as effective as vancomycin. Vancomycin was more effective than placebo (P=0.03) in a small study (N=21). With regards to symptomatic cure, metronidazole, bacitracin and fusidic acid were found similar to vancomycin. Teicoplanin was slightly more effective than vancomycin (P=0.06). For initial bacteriologic resolution, vancomycin was more effective than placebo (P=0.03); teicoplanin was more effective than vancomycin (P=0.002); and metronidazole, fusidic acid, and rifaximin were as effective as vancomycin (P=0.008). In terms of bacteriologic cure, in comparison with vancomycin, teicoplanin was more effective (P=0.006), metronidazole was as effective (P=0.07), and fusidic acid was less effective (P=0.01). Patients were retreated in various ways, which made it difficult to compare the antibacterials for efficacy. There were a total of 9 deaths, 5 of which were specified to be due to underlying illness and not related to treatment. Secondary: These end points occurred infrequently in all of the studies.
Zar et al.[95] (2007) Vancomycin 125 mg orally 4 times per day for 10 days	RCT, DB, PC Patients with *Clostridium difficile*-associated diarrhea (CDAD)	N=172 21 days	Primary: Clinical cure	Primary: Among the patients with mild CDAD, treatment with metronidazole or vancomycin resulted in clinical cure in 90% and 98% of the patients, respectively (P=0.36). Among the patients with severe CDAD, treatment with metronidazole or vancomycin resulted in clinical cure in 76% and 97% of the patients,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs metronidazole 250 mg orally 4 times per day for 10 days				respectively (P=0.02). Clinical symptoms recurred in 15% of the patients treated with metronidazole and 14% of those treated with vancomycin.
Nelson[96] (2007) Vancomycin vs metronidazole, fusidic acid, nitazoxanide, teicoplanin, rifampin, rifaximin, bacitracin	MA Patients with *Clostridium difficile*-associated diarrhea (CDAD)	N=1157 (12 RCT) Variable duration	Primary: Clinical cure	Primary: No single antibiotic was clearly superior to others. Teicoplanin showed in some outcomes significant benefit over vancomycin and fusidic acid, and a trend towards benefit compared to metronidazole. Only one placebo controlled trial was done and no conclusions can be drawn from it due to small size and classification error. Only one study investigated synergistic antibiotic combination, metronidazole and rifampin, and there was no advantage to the drug combination.
Genitourinary Infections				
Ugwumadu et al.[35] (2003) Clindamycin 300 mg PO BID vs placebo	RCT, DB, PC Pregnant women ≥12-22 weeks gestation with abnormal vaginal flora or bacterial vaginosis	N=485 5 days	Primary: Spontaneous preterm delivery (birth ≥24 but <37 weeks) and late miscarriage (pregnancy loss ≥13 but <24 weeks)	Primary: Incidence of spontaneous preterm delivery was 11/244 (5%) in the clindamycin group vs 28/241(12%) in the placebo group; incidence of miscarriage was 2/244 (1%) in the clindamycin group vs 10/241(4%) in the placebo group (P=0.001 for both). Overall, women receiving clindamycin had significantly fewer miscarriages or spontaneous preterm deliveries than did those in the placebo group. Adverse events included gastrointestinal upset (5 patients receiving clindamycin vs 10 receiving placebo), rash (1 patient receiving clindamycin vs 2 receiving placebo), vulvovaginal candidiasis (1 patient receiving clindamycin vs 1 receiving placebo), throat irritation (1 patient receiving placebo), and headache (4 patients receiving clindamycin vs 1 receiving placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall, there was no statistically significant difference in reported adverse events (P=0.10).
Mahakit et al.[38] (2006) Clindamycin 300 mg PO BID vs amoxicillin-clavulanic acid 875/125 mg BID	PRO, MC, SB, RCT Patients 12-60 years of age with acute recurrent pharyngotonsillitis caused by group A β-hemolytic streptococci (GABHS)	N=772 Treatment: 10 days Follow-up: 30 months posttreatment	Primary: Clinical cure; clinical cure with recurrence; clinical improvement; clinical failure; adverse event failure; bacteriologic eradication; bacteriologic persistence; bacteriologic recurrence Secondary: Safety profile of each regimen	Primary: Of clinically evaluable patients (560), 18 had missing assessments at day 12; in the remaining population (N=542) 92.6% of clindamycin-treated patients had a clinical cure vs 85.2% in the amoxicillin-clavulanic acid group (P<0.003). Clinical failures were documented in 7.4% and 14.8% of patients receiving clindamycin and amoxicillin-clavulanic acid, respectively. After 3 months, the clinical cure rate in evaluable patients (N=559) was 95.4% vs 95.7% with clindamycin and amoxicillin-clavulanic acid, respectively (P=0.172). There was no statistically significant difference between groups in terms of bacteriologic efficacy at day 12 or at 3 months follow-up. Secondary: The most commonly occurring adverse drug-related event involved the digestive system. Diarrhea was noted in 8.6% (33/383) of patients that received clindamycin and 5.6% (22/389) of patients that received amoxicillin-clavulanic acid (P=NS). No adverse event resulted in early treatment discontinuation. A total of 772 patients took >1 dose of study medication; 757 patients remained in the study at day 4, 560 at day 12, and 532 at 3 month follow-up.
French et al.[34] (2004) Clindamycin plus an aminoglycoside vs	MA Women with postpartum endometritis, after cesarean section or vaginal birth	N=1,902 Variable duration	Primary: Treatment failure	Primary: Nineteen studies comparing clindamycin plus an aminoglycoside (usually gentamicin) with an alternative regimen demonstrated more treatment failures with the other regimen (RR=1.44, 95% CI, 1.15 to 1.8). The overall failure rate of clindamycin plus gentamicin was 11.4% (106/928).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
various alternative antibacterial regimens				The incidence of diarrhea was more common with the clindamycin regimens, though not at a statistically significant level (95% CI, 0.35 to 1.25). Seven studies (N=741) compared a second or third generation cephalosporin with another regimen (usually clindamycin plus gentamicin) and demonstrated no difference in treatment failures between groups (RR=1.39, 95% CI, 0.90 to 2.15). The incidence of diarrhea was less frequent with the cephalosporin group. Four trials (N=603) compared aztreonam plus clindamycin with other regimens (i.e., clindamycin plus gentamicin or trospectomycin) and did not reveal evidence of a difference between groups. One trial (N=97) investigated the difference between ciprofloxacin and clindamycin plus gentamicin and demonstrated more treatment failures in the ciprofloxacin group, though not at a statistically significant level (RR=1.96, 95% CI, 0.20 to 4.21).
Arredondo et al.[36] (1997) Clindamycin PO plus ciprofloxacin PO vs ceftriaxone IM plus doxycycline PO	MC, PRO, DB Women with mild to moderate pelvic inflammatory disease	N=131 Precise duration of therapy not specified	Primary: Clinical cure	Primary: Both regimens were similar in efficacy with a clinical cure rate of 97% (65/67) in the clindamycin group vs 95% (61/64) in the ceftriaxone group.
Blanco et al.[37] (1983) Clindamycin 600 mg IV every 8 hours plus tobramycin 1.5	PRO, OL, RCT Women with a clinical diagnosis of endometritis, salpingitis, or pelvic cellulitis after	N=77 Precise duration of therapy not specified	Primary: Clinical cure, therapeutic failure (persistent fever and tenderness at infected site despite 72 hours of	Primary: Clinical outcome was not statistically different between groups. 34/39 (87.2%) patients in the clindamycin group responded to treatment and 34/38 (89.5%) in the ceftazidime group responded well. All clinical failures occurred in patients who had endometritis following cesarean section.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg IV every 8 hours vs ceftazidime 2 g IV every 8 hours	hysterectomy with temperature ≥ 38ºC, leukocytosis, and local tenderness		treatment), or side effect failure	One patient developed urticaria/rash on clindamycin therapy, but had responded to treatment at this time; rash was resolved upon drug discontinuation. No patients developed diarrhea.
Hepatic Encephalopathy				
Bass et al.[100] (2010) Rifaximin 550 mg BID vs placebo Concomitant use of lactulose was allowed throughout the study.	RCT, DB, PC Patients ≥18 years of age who had ≥2 episodes of overt hepatic encephalopathy (Conn score, ≥2) associated with hepatic cirrhosis during the previous 6 months, remission (Conn score, 0 or 1) at enrollment, and a score of ≤25 on the Model for End-Stage Liver Disease (MELD) scale	N=299 6 months	Primary: Time to the first breakthrough episode of hepatic encephalopathy Secondary: Time to the first hospitalization involving hepatic encephalopathy and safety	Primary: Breakthrough episodes of hepatic encephalopathy were reported in 22.1% of patients receiving rifaximin and 45.9% of patients in the placebo group (HR, 0.42; 95% CI, 0.28 to 0.64; P<0.001). Four patients would need to be treated with rifaximin for 6 months to prevent one episode of overt hepatic encephalopathy. Secondary: Hospitalization involving hepatic encephalopathy occurred in 13.6% of patients receiving rifaximin and 22.6% of patients receiving placebo (HR, 0.50; 95% CI, 0.29 to 0.87; P=0.01). Nine patients would need to be treated with rifaximin for 6 months to prevent one hospitalization involving hepatic encephalopathy. The incidence of adverse events reported during the study was similar in the rifaximin group (80.0%) and the placebo group (79.9%). A total of 20 patients died during the study (9 in the rifaximin group and 11 in the placebo group). Most of the deaths were attributed to conditions associated with disease progression.
Williams et al.[101] (2000) Rifaximin 200 mg TID vs rifaximin 400 mg TID	RCT, DB, PG, MC Patients with cirrhosis and mild to moderate hepatic encephalopathy (HE) who had experienced recent deterioration in their neuropsychiatric	N=54 7 days	Primary: Change in the portal-systemic encephalopathy (PSE) index (calculated on the basis of asterixis, number connection test (NCT) time, EEG	Primary: There was a significant reduction in the mean PSE index in the rifaximin 1,200 mg/day and 2,400 mg/day groups (95% CI, -17.4 to -3.1 and -17.8 to -3.6, respectively). Mean values for blood ammonia levels on days 1 and 7, respectively, were 132.8 and 107.1 in the rifaximin 600 mg/day group, 143.5 and 143.0 in the 1,200 mg/day group, and 183.3 and 188.6 in the 2,400 mg/day group. Rifaximin was well tolerated. Nausea and gastrointestinal system disorders

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rifaximin 800 mg TID	status		mean cycle frequency and blood ammonia concentrations)	were the most frequent adverse events.
Bucci et al.[102] (1993) Rifaximin 400 mg TID vs lactulose 10 g TID	RCT, DB Patients 42-60 years of age with cirrhosis and signs/symptoms of portosystemic encephalopathy	N=58 15 days	Primary: Mental status using Parsons-Smith point scale, presence of asterixis, 'A' cancellation test, Reitan test, electro-encephalographic irregularities, adverse events	Primary: There was an improvement in cognitive function in both groups. Patients receiving rifaximin had a significant improvement starting on day 6 (P<0.05), and those receiving lactulose had a significant improvement starting on day 12 (P<0.01). Starting on day 9, the comparison between the two groups was significantly in favor of rifaximin (P<0.01). The presence of asterixis decreased in both groups. There was a significant difference for both treatments starting on day 9 compared to baseline (P<0.01). There was no significant difference between the groups. The 'A' cancellation test showed a progressive improvement in the two groups. The difference became significant starting on day 6 with rifaximin and day 9 with lactulose compared to baseline. The Reitan test showed good recovery of manipulation. There was no significant difference between the treatment groups. Improvement was noted starting on day 9 in both groups. There was a significant improvement in electroencephalographic irregularities at day 6 with rifaximin and day 9 with lactulose. The difference between the two treatment groups was significant on day 6 (P<0.05), as well as days 12 and 15 (P<0.01). There was a significant reduction in fasting ammonia levels beginning on day 5. Levels were normal after 7 days with both treatments. The comparison between the two treatments was significantly in favor of rifaximin on days 3, 5 and 12 (P<0.05). Diarrhea, flatulence and dyspepsia appeared in 50% of patients treated with lactulose. In those treated with rifaximin, the frequency and severity of the adverse events was minimal. Body weight decreased in 28.6% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				those treated with lactulose and in 6.7% of those treated with rifaximin.
Paik et al.[103] (2005) Rifaximin 400 mg TID vs lactulose 90 ml/day	RCT, OL In-patients with episodic hepatic encephalopathy (HE) who had decompensated liver cirrhosis and stage 1 to 3 HE (according to Conn's modification of Parsons-Smith classification) and serum ammonia levels >75 µmol/L	N=54 7 days	Primary: Grade of mental state, severity of flapping tremor, number connection test (NCT), blood ammonia levels, HE index, and efficacy of treatment	Primary: Mean blood levels and grades of blood NH_3 significantly decreased with rifaximin (P<0.01) and lactulose (P<0.01). Mean blood NH_3 concentrations were similar after both treatments. Mental state was significantly improved by rifaximin and by lactulose (P<0.01 and P<0.01, respectively). Grades of flapping tremor and NCT were improved to a similar degree by rifaximin and lactulose. Mean HE indexes improved in the rifaximin group (P=0.000) and in the lactulose group (P=0.000). There was no significant difference between the treatment groups. Blood NH_3 and HE grades improved in 78.1% and 81.3%, respectively, of the patients in the rifaximin group. In the lactulose group, 59.1% of the patients showed reduced blood ammonia grades and 72.7% showed improved HE grades. There was no significant difference between the treatment groups. Rifaximin was considered effective in 84.4% of patients and lactulose was considered effective in 95.4% of patients (P=0.315). One patient treated with rifaximin complained of abdominal pain, and one patient treated with lactulose experienced severe diarrhea.
Neff et al.[104] (2006) Rifaximin 1,200 mg/day vs lactulose 60 g/day, titrated as	RETRO Patients with end-stage liver disease and stage 1 or 2 hepatic encephalopathy	N=39 Variable duration	Primary: Hospitalizations and length of stay	Primary: There were 19 total hospitalizations in the lactulose group (9 patients) and 3 hospitalizations in the rifaximin group. The average length of stay was shorter in the rifaximin group at 3.5 days compared to 5.0 days in the lactulose group (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
necessary				
Leevy et al.[105] (2007) Lactulose 30 ml BID for ≥6 months, then rifaximin 400 mg TID for ≥6 months	RETRO Patients with hepatic encephalopathy	N=146 ≥6 months	Primary: Mean number of hospitalizations during each treatment period Secondary: Average length of hospitalization, mean total time hospitalized, clinical status	Primary: There were fewer hospitalizations during the rifaximin period compared with the lactulose period (0.5 vs 1.6; P<0.001). Secondary: There were fewer days of hospitalization (2.5 vs 7.3; P<0.001) and fewer total weeks hospitalized (0.4 vs 1.8; P<0.001) during the rifaximin period compared with the lactulose period. Hepatic encephalopathy grade at the end of each treatment period reflected less severe illness with rifaximin than with lactulose (P<0.001). The percentage of patients with stage 3 or 4 hepatic encephalopathy was 6% with rifaximin and 25%with lactulose. Significantly fewer patients had asterixis at the end of the rifaximin period (63%) than the lactulose period (93%; P<0.001). The percentages of patients with diarrhea, flatulence, and abdominal pain were significantly higher during the lactulose period than the rifaximin period (all, P<0.001). The percentage of patients with headache did not differ between treatment periods (P=0.718).
Mas et al.[106] (2003) Rifaximin 400 mg TID vs lactitol 20 g TID	RCT, DB Patients with grade I-III acute hepatic encephalopathy for <2 days duration and a portal-systemic encephalopathy (PSE) index higher than zero	N=103 5-10 days	Primary: Efficacy and safety	Primary: There were significant improvements in hepatic encephalopathy (HE) endpoints and ammonemia levels following treatment with rifaximin and lactitol. There was no significant difference between the treatment groups at the end of therapy (HE grade, P=0.9211; mental state, P=0.8480; asterixis, P=0.3177; NCT in seconds, P=0.7810; EEG counts/second, P=0.092). The overall PSE index decreased more progressively in the rifaximin group than in the lactitol group (P<0.01). With regards to the global assessment of efficacy at the end of treatment; both groups showed a similar clinical efficacy without significant differences. After grouping the responses into two classes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(resolution/improvement vs unchanged/failure), the results were similar in both groups: 81.6% vs 18.4%, respectively, in the rifaximin group and 80.4% vs 19.6%, respectively, in the lactitol group. The percentage of patients with complete HE resolution was higher in the rifaximin group (53.1%) than in the lactitol group (37.2%). Both treatments were well tolerated. In the rifaximin group, 2 patients reported mild diarrhea and 1 patient reported abdominal pain. In the lactitol group, 1 patient reported mild diarrhea and 1 described vomiting.
Jiang et al.[107] (2008) Rifaximin vs nonabsorbable disaccharides	MA Patients ≥18 years of age with serum ammonia levels ≥75 µmol/L, signs and symptoms of acute, chronic, or minimal hepatic encephalopathy	N=264 (5 trials) Variable duration	Primary: Clinical efficacy Secondary: Adverse events	Primary: There was no significant difference in clinical efficacy for hepatic encephalopathy between rifaximin and nonabsorbable disaccharides (RR, 1.08; 95% CI, 0.85–1.38; P=0.53). Secondary: Diarrhea and abdominal pain were the most frequently reported adverse events. There was no difference in diarrhea between the treatment groups (RR=0.90; 95% CI, 0.17–4.70; P=0.90). A significant difference on abdominal pain was noted (RR, 0.28; 95% CI, 0.08–0.95; P=0.04).
Festi et al.[108] (1993) <u>Study 1</u> Rifaximin 1,200 mg/day for 21 days <u>Study 2</u> Rifaximin 1,200 mg/day for 21 days vs neomycin 3,000 mg/day for 21 days <u>Study 3</u>	OL (Study 1), RCT (Study 2 and 3) Patients 40-75 years of age with clinical and biochemical signs of mild hepatic encephalopathy and liver cirrhosis	N=136 21 days	Primary: Neurological signs, electro-encephalographic (EEG) abnormalities, ammonia levels	Primary: <u>Study 1</u> Rifaximin significantly reduced the frequency of neurologic signs. After 5 days of treatment, the percentage of patients who exhibited asterixis was significantly lower than at baseline; after 15 days of treatment, no patients showed this neurologic sign. After 7 days, a significantly lower percentage of patients exhibited EEG abnormalities. Blood ammonia levels were significantly improved with rifaximin after 5 days. Blood ammonia concentrations reached normal values and remained within the normal range throughout the study. <u>Study 2</u> Both rifaximin and neomycin reduced the neurologic signs of hepatic encephalopathy, but at different rates. Treatment with rifaximin led to a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rifaximin 1,200 mg/day for 21 days vs lactulose 40 g/day for 21 days				significant reduction in the frequency of asterixis after 3 days compared to 5 days with neomycin. A significantly lower percentage of patients exhibited EEG abnormalities with rifaximin and neomycin compared to baseline (P<0.001). Ammonia levels were significantly reduced by rifaximin and neomycin. Normal values were achieved after 7 days of treatment. <u>Study 3</u> Both rifaximin and lactulose reduced the neurologic signs of hepatic encephalopathy compared to baseline (P<0.05). EEG abnormalities significantly decreased in frequency with rifaximin and lactulose compared to baseline. Ammonia levels were significantly decreased with both treatments (P<0.01).
Miglio et al.[109] (1997) Rifaximin 400 mg TID for 14 days each month vs neomycin 1 g TID for 14 days each month	RCT, DB Patients with cirrhosis and chronic hepatic encephalopathy of grade 1 or 2	N=60 6 months	Primary: Improvement of at least 1 grade of hepatic encephalopathy (HE), neurological signs, Reitan test, ammonia levels, liver function tests	Primary: There was a progressive reduction in HE grade with rifaximin and neomycin. There was no significant difference between the two treatment groups. The improvement in HE was significant after 30 days (P<0.001 for each group). In both groups, the disturbances in speech, memory, behavior and mood, gait, asterixis, writing, serial subtraction of 7s and five-pointed star tests showed the highest improvement (P<0.001). The Reitan test only showed a significant improvement in the rifaximin group (P<0.02). Blood ammonia levels were decreased from 210.2 to 88.9 mcg/100 ml in the rifaximin group (P<0.001) and from 202.1 to 86.2 mcg/100 ml in the neomycin group (P<0.001). There was no significant difference between the treatment groups. There were significant decreases in AST (P<0.02) and ALT (P<0.01 in the rifaximin group and P<0.03 in the neomycin group).
Sidhu et al.[115]	RCT, DB, PC	N=284	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) Rifaximin 400 mg three times daily for 8 weeks vs placebo	Patients 18 to 65 years of age with cirrhosis and minimal hepatic encephalopathy (MHE)	8 weeks	Reversal of MHE at 8 weeks Secondary: Reversal of MHE at 2 weeks and improvement in HRQOL at 8 weeks	In the ITT analysis, the percentage of patients showing reversal of MHE was significantly higher in rifaximin group than in the placebo group (75.5% vs 20%, respectively; P<0.0001). Secondary: Rifaximin led to a significant reduction in 7 of the 12 scales of SIP score, total psychosocial and physical sub-scores, and the total SIP score after 8 weeks of treatment. The changes in SIP scores in placebo group were not significant. One patient in rifaximin group and two in placebo group developed OHE (P=0.605). Two patients in rifaximin group reported epigastric discomfort and vomiting after 7 and 15 days of randomization. None of the patients in placebo group reported any side effect (P=0.495). Rifaximin group showed a significant reduction in the percentage of patients having abnormal NCT, PCT and BDT after 2 weeks and abnormal NCT, FCT, PCT and BDT after 8 weeks. Rifaximin group also showed significant reduction in mean number of abnormal NP tests (baseline, 2.35 (95% CI, 2.17 to 2.53); 2 weeks, 1.29 (95% CI, 1.02 to 1.56), P=0.002; 8 weeks, 0.81 (95% CI, 0.61 to 1.02), P=0.000), compared with placebo group (baseline, 2.31 (95% CI, 2.03 to 2.59); 2 weeks, 2.03 (95% CI, 1.74 to 2.31); 8 weeks, 1.97 (95% CI, 1.69 to 2.25), P>0.05). Rifaximin group showed a significant reduction in the mZS after 2 and 8 weeks, compared with baseline. The reduction in mZs in placebo group was not significant. The mean total SIP score improved significantly in rifaximin group (baseline, 11.67 (95% CI, 10.31 to 13.03); 8 weeks, 6.45 (95% CI, 5.59 to 7.30); P=0.000) compared with placebo group (baseline, 9.86 (95% CI, 8.66 to 11.06); 8 weeks, 8.51 (95% CI, 7.35 to 9.67); P=0.82).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Improvement in HRQOL correlated with improvement in NP tests. Rifaximin was well tolerated.
Respiratory Infections				
Toma et al.[39] (1998) Clindamycin 450 mg IV/PO plus primaquine 15 mg PO every 6 hours vs sulfamethoxazole-trimethoprim (SMZ-TMP) 240 mg/1,200 mg (if <60 kg) or 320 mg/1,600 mg (if ≥60 kg) plus placebo every 6 hours	MC, DB, RCT Individuals >16 years old with HIV-related *Pneumocystis carinii* pneumonia (PCP), with plasma partial oxygen pressure (PaO_2) >50 mm Hg, and body weight >45 kg	N=87 21 days	Primary: Success of treatment (defined as decrease of ≥2 points in the PCP score and overall scores lower than baseline, with no ventilator use, no switch to alternate therapy, and no steroid use after day 4 of therapy), survival for ≥35 days after therapy initiation, relapse rate (defined as recurrence of clinical signs/symptoms or radiographic changes suggesting PCP)	Primary: Overall success rate was 76% (34/45) in the clindamycin group vs 79% (33/42) in the SMX-TMP group. For patients with PaO_2 ≤70 mm Hg, success rate was 74% in the clindamycin group and 76% in the SMX-TMP group (95% CI, 2 ± 25%). Hematotoxic events were most common in both treatment groups. Overall adverse event rate was less in the clindamycin group (13 patients vs 21 patients; P=0.04). Initial sample size of 180 was needed to detect a difference with a power of 0.8. After confirmation of PCP, primary analysis was based on 87 patients, with a separate analysis done for patients with moderately severe PCP (patients with PaO_2 ≤70 mm Hg).
Allewelt et al.[40] (2004) Clindamycin 600 mg IV TID (then 300 mg PO TID) ± second or third generation cephalosporin vs	OL, MC, RCT Inpatients ≥18 years old with aspiration pneumonia and/or pulmonary abscess	N=70 22-24 days	Primary: Clinical response (complete or partial resolution of radiographic abnormalities and complete normalization of clinical signs and laboratory parameters of	Primary: Clinical response at the end of therapy in the ampicillin-sulbactam group was 73% vs 66.7% in the clindamycin group. Clinical response at 7 to 14 days after therapy was 67.6% in the ampicillin-sulbactam group vs 63.6% in the clindamycin group. Bacteriologic response was evaluated in 44 patients, with inconclusive results due to the small number of cases. Treatment failure leading to premature discontinuation occurred in 8

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ampicillin 2 g/ sulbactam 1 g IV TID (then 750 mg PO BID)			infection), failure (persistence, relapse and reinfection)	patients (19.5%) receiving ampicillin-sulbactam and in 10 patients (24.4%) receiving clindamycin therapy.
Raad et al.[41] (2001) Clindamycin 900 mg IV plus aztreonam 2 g IV every 8 hours vs piperacillin-tazobactam 4.5 g IV every 6 hours	PRO, RCT Non-neutropenic adults >18 years of age with cancer and nosocomial pneumonia	N=53 6 to 8 days	Primary: Clinical response (complete resolution of signs/symptoms of pneumonia), superinfection	Primary: Response rate was 86% (19/22) in the clindamycin group and 83% (25/30) in the piperacillin-tazobactam group (P>0.99). Patients receiving clindamycin generally required a greater duration of therapy (mean days of therapy 8.1 vs 6.8; P=0.1). For gram-positive infections, both regimens had a 100% response rates. For nosocomial gram-negative infections, there was a 75% response rate for clindamycin-treated patients compared to a 67% response rate with piperacillin-tazobactam (P=0.53). Adverse events and superinfections did not differ by treatment group (P>0.3).
San Pedro et al.[44] (2002) Linezolid 600 mg IV then PO BID vs ceftriaxone 1 g IV BID then cefpodoxime 200 mg PO BID Aztreonam 1-2 g IV every 8 hours was given at the discretion of the investigator.	OL, MC, RCT Patients ≥13 years of age with signs and symptoms of pneumonia	N=747 Treatment: 7-14 days Follow-up: 12-28 days posttreatment	Primary: Clinical outcomes (cure, failure, indeterminate, or missing), microbiologic outcomes (eradication, non-eradication, indeterminate, or missing)	Primary: In the ITT population, the clinical cure rate was 83% with linezolid vs 76.4% with the cephalosporins (P=0.04). In the evaluable-SP/bacteremia population (patients with *S pneumonia)*, the clinical cure rate was 93.1% with linezolid vs 68.2% with the cephalosporins (P=0.021). The clinical cure rates for the other populations were not statistically different. *S pneumoniae* eradication rates were similar in both groups (P=0.83). 54.3% of linezolid-treated patients received concomitant aztreonam compared with 2.2% of the cephalosporin-treated patients. The most common reason for treatment discontinuation was lack of efficacy, with higher rates of withdrawal in the cephalosporin group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(7.1%) compared to the linezolid group (3.7%). Incidence of adverse events was 21.3% with linezolid vs 11.2% with the cephalosporins (P=0.0002).
Rubinstein et al.[42] (2001) Linezolid 600 mg IV every 12 hours vs vancomycin 1 g IV every 12 hours Both regimens included aztreonam 1-2 g IV every 8 hours.	MC, DB, RCT Patients ≥18 years of age with nosocomial pneumonia	N=396 Treatment: 7-21 days Follow-up: 12-28 days posttreatment	Primary: Cure, failure, microbiological success or failure	Primary: Rates of clinical cure for the ITT population were 53.4% (86/161) vs 52.1% (74/142) with linezolid and vancomycin, respectively (P=0.79). In the clinically evaluable population, clinical cure rate was 66.4% (71/107) with linezolid and 68.1% (62/91) with vancomycin (P=0.79). Microbiological success rate was 67.9% (36/53) with linezolid and 71.8% (28/39) with vancomycin (P=0.69). Safety assessments were done for the ITT population. Diarrhea was more frequent in linezolid recipients (4.4% vs 2.6%); however, abnormal liver function tests were more common with vancomycin (1.6% vs 1%) as was incidence of rash (1.6% vs 0). There were 36 deaths in the linezolid group and 49 with vancomycin (17.7% vs 25.4%, respectively; P=0.06).
Wunderink et al.[43] (2003) Linezolid 600 mg IV every 12 hours vs vancomycin 1 g IV every 12 hours Patients could have also received aztreonam 1-2 g IV every 8 hours.	MC, DB, RCT Patients >18 years of age with pneumonia acquired 48 hours after admission to an inpatient facility	N=345 Treatment: 7-21 days Follow-up: 15-21 days posttreatment	Primary: Clinical outcomes (cure or failure) and microbiologic outcomes (success and failure) at follow-up visit	Primary: 55.4% of total enrolled patients (345/623) were clinically evaluable. Clinical cure rates were equivalent between linezolid- and vancomycin-treated patients (67.9% and 64.9%, respectively; P=NS). 25.5% of total patients (159/623) were microbiologically evaluable. Microbiological success rates were similar between linezolid- and vancomycin-treated patients (61.8% and 53.2%, respectively; P=NS). More patients had multiple-lobe involvement in the linezolid group vs the vancomycin group (56.1% vs 44.3%; P=0.004).
Wunderink et al.[91]	RCT, OL, MC	N=149	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) Linezolid 600 mg every 12 hours vs vancomycin 1 g every 12 hours	Patients with methicillin-resistant *Staphylococcus aureus* (MRSA) ventilator-associated pneumonia (VAP)	30 days	Microbiological response and clinical cure Secondary: Clinical outcome, mortality, ventilator use at the end of therapy and follow-up visits, health resource outcomes (duration of mechanical ventilation, hospitalization, and ICU stay)	Due to the limited number of patients per treatment group, the study did not have sufficient power to establish non-inferiority between linezolid and vancomycin for the primary end point. Overall, 56.5% of linezolid-treated patients achieved a microbiological cure compared to 47.4% of vancomycin-treated patients (P= 0.757; 95% CI, -21.1 to 39.4). Clinical cure was demonstrated in 66.7% of linezolid-treated patients compared to 52.9% of vancomycin-treated patients (P=0.375). Secondary: The survival rate (86.7% vs 70.0%, respectively) mean duration of ventilation (10.4 vs 14.3 days, respectively), hospitalization (18.8 vs 20.1 days, respectively), ICU stay (12.2 vs 16.2 days, respectively), and time spent alive and not receiving mechanical ventilation (15.5 vs 11.1 days, respectively) were not significantly different between linezolid-treated patients and vancomycin-treated patients.
Kaplan et al.[45] (2003) Linezolid IV then PO vs vancomycin IV then appropriate PO agent	RCT Hospitalized children (birth to 12 years old) with antibiotic-resistant gram-positive infections (nosocomial pneumonia, complicated skin and skin structure infections, catheter-related bacteremia, and other infections)	N=321 10-28 days	Primary: Clinical cure rate and pathogen eradication rate	Primary: Clinical cure rate was 74% with vancomycin and 79% with linezolid in the intent-to-treat population (P=0.36). The cure rate in the clinically evaluable population was 85% and 89% with vancomycin and linezolid, respectively (P=0.31). Eradication rates for methicillin-resistant *S aureus* were similar for both groups (P=0.89). Patients receiving linezolid required fewer days of IV therapy (P<0.001) and experienced fewer adverse drug events (P=0.003).
Fagon et al.[46] (2000) Quinupristin-	OL, MC, RCT Patients ≥18 years developing	N=171 5-14 days	Primary: Clinical response at test-of-cure assessment (7-13	Primary: Therapy was clinically successful in 58.3% of patients receiving vancomycin and 56.3% of patients receiving quinupristin-dalfopristin (-2% difference [95% CI, -16.8% to 12.8%]).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dalfopristin 7.5 mg/kg IV every 8 hours vs vancomycin 1 g IV every 12 hours Aztreonam, imipenem, or tobramycin were added if determined clinically necessary.	sufficiently severe nosocomial pneumonia that required ≥5 days of parenteral antibiotics		days after end of treatment if cure/improvement; 13 days after end of treatment if failure) in the bacteriologically evaluable population (by-pathogen bacteriologic response, by-patient bacteriologic response) Secondary: Clinical response for the all-treated population	The by-pathogen bacteriologic response was similar between treatment groups (for *S pneumoniae, S aureus*, MRSA). The by-patient bacteriologic success rate was 64.3% and 58.6% in the vancomycin and quinupristin-dalfopristin groups, respectively (-5.7% difference [-20.2% to 8.9%]). 32 patients died in the vancomycin group compared to 38 patients in the quinupristin-dalfopristin group (P=0.45). Secondary: The clinical success rate was similar between groups in the all-treated population (45.3% for vancomycin and 43.3% for quinupristin-dalfopristin (-1.9% difference [-13.2% to 9.3%]). There was no statistically significant difference between groups in reported adverse events (P=NS).
Rubinstein et al.[127] (2011) Telavancin 10 mg/kg IV once daily for 7 to 21 days vs vancomycin 1 g IV twice daily for 7 to 21 days	RCT, DB, AC (2 trials) Patients ≥18 years of age with hospital-acquired pneumonia due to gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA)	N=1,503 7 to 14 days posttreatment	Primary: Clinical response at the follow-up/test-of-cure (FU/TOC) visit (7 to 14 days after treatment)	Primary: In all treated patients at the FU/TOC visit (study 0015), cure rates were 57.5% with telavancin and 59.1% with vancomycin (95% CI, -8.6 to 5.5). In study 0019, cure rates were 60.2% with telavancin and 60.0% with vancomycin (95% CI, -6.8 to 7.2). In the clinically evaluable population at the FU/TOC visit (study 0015), cure rates were 83.7% with telavancin and 80.2% with vancomycin (95% CI, -5.1 to 12.0). In study 0019, cure rates were 81.3% with telavancin and 81.2% with vancomycin (95% CI, -8.2 to 8.4). In the pooled all treated population, cure rates with telavancin were 58.9% compared to 59.5% with vancomycin (95% CI, –5.6 to 4.3). In the pooled clinically evaluable population, cure rates were 82.4% with telavancin and 80.7% with vancomycin (95% CI, –4.3 to 7.7). In patients with pneumonia due to *S. aureus*, the clinical response at the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				FU/TOC visit was 78.1% with telavancin compared to 75.2% with vancomycin; 95% CI, -9.5 to 10.4). In patients with pneumonia due to MRSA, with or without other pathogens, the clinical response at the FU/TOC visit was 74.8% with telavancin compared to 74.7% with vancomycin; 95% CI, -9.5 to 10.4). The incidence and types of adverse events were comparable between the treatment groups. Mortality rates with telavancin were 21.5% compared to 16.6% with vancomycin (95% CI, –0.7 to 10.6) for study 0015. Mortality rates were 18.5% with telavancin compared to 20.6% with vancomycin (95% CI, –7.8 to 3.5) for study 0019. Increases in serum creatinine level were more common in the telavancin group (16% vs 10%).
Miscellaneous Infections				
Peltola et al.[47] (1997) Clindamycin 40 mg/kg/day IV divided into four doses vs first generation cephalosporin (cephradine until withdrawn from the Scandinavian market; then cephalothin) 150 mg/kg/day divided into four doses	PRO, MC, RCT Patients 3 months to 14 years of age with acute osteomyelitis	N=50 Treatment: 3-4 weeks Follow-up: Up to 27 months	Primary: Patients achieving full recovery and remaining healthy ≥12 months from hospital discharge	Primary: C-reactive protein normalized within 9 days and the sedimentation rate normalized within 29 days. Mean duration in hospital was 11 days. At long-term follow-up, all signs and symptoms resolved in each patient with no growth, other long-term sequelae, or relapse. Treatment initiated IV then switched to PO within approximately 4 days (clindamycin PO vs cefadroxil PO).
Linden et al.[48] (2003) Colistin	PRO Critically ill patients (organ recipients as	N=23 7-36 days	Primary: Favorable response, defined as complete or	Primary: Favorable clinical response was observed in 14 patients (61%). Seven patients died during therapy (30.4%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(colistimethate) dose based on weight	well as other non-transplant general surgery patients) with multi-drug resistant *P aeruginosa* infection		partial resolution of signs and symptoms at end of treatment; unfavorable response, defined as persistence or worsening of signs and symptoms or death	Majority of patients enrolled had pneumonia (n=18) or intra-abdominal infection (n=5). *P aeruginosa* bacteremia was associated with clinical failure (P=0.02).
Kasakou et al.[49] (2005) Colistin (colistimethate) 1.5 to 9 million IU IV per day Colistin was used as monotherapy or in combination with other antimicrobials.	RETRO Hospitalized patients with multi-drug resistant gram-negative bacilli managed with colistin for ≥72 hours	N=50 4 to 72 days	Primary: Mortality Secondary: Clinical outcome of infection, occurrence of renal dysfunction	Primary: In-hospital mortality was 24% (12/50); age and temperature upon hospital admission were independent predictors of mortality. Secondary: Four patients developed two episodes of infection and were treated as two different cases. A total of 53.7% (29/54) had a cure and 13% (7/54) showed improvement and 33.3% (18/54) were unresponsive. Deterioration of renal function was noted in 8% (4/50) of patients receiving colistin. A total of 6/50 patients received colistin by an alternate route in addition to IV (intraventricular, nebulized, or irrigation solution). A total of 31/50 patients had concurrent administration with one or two additional agents such as, meropenem (60%), ampicillin-sulbactam (34%), ciprofloxacin (20%), piperacillin-clavulanic acid (20%), imipenem (16%), or amikacin plus gentamicin (14%).
Fowler et al.[31] (2006) Daptomycin 6 mg/kg IV QD	MC, OL, RCT Patients with *S aureus* bacteremia with or without endocarditis	N=235 Variable duration	Primary: Clinical success rate in each group of the modified intention-to-treat population at 42	Primary: In the modified intention-to-treat (ITT) population, successful outcome was noted in 53/120 patients in the daptomycin group (44.2%) vs 48/115 patients in the standard-therapy group (41.7%). Directly following the end of therapy, success rates were 61.7% and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs standard therapy (vancomycin 1 g every 12 hours, or nafcillin, oxacillin, flucloxacillin 2 g every 4 hours)			days after end of therapy, failure (clinical failure, microbiologic failure, death, failure to obtain blood culture, receipt of potentially effective non-study antibiotics, or premature discontinuation)	60.9% in the daptomycin and standard therapy groups, respectively. The baseline pathogen was determined to be methicillin-resistant *S aureus* (MRSA) in 37.5% and 38.3% of patients in the daptomycin and standard therapy groups, respectively. In the daptomycin group, patients were diagnosed with uncomplicated bacteremia (26.7%), complicated bacteremia (50%), uncomplicated right-sided endocarditis (5%), complicated right-sided endocarditis (10.8%), or left-sided endocarditis (7.5%). In the standard therapy group, patients were diagnosed with uncomplicated bacteremia (25.2%), complicated bacteremia (53%), uncomplicated right-sided endocarditis (3.5%), complicated right-sided endocarditis (10.4%), or left-sided endocarditis (7.8%). Patients infected with MRSA had a higher success rate with daptomycin vs standard therapy, though this was not a statistically significant difference (44.4% vs 31.8%; P=0.28). Patients infected with methicillin-susceptible *S aureus* (MSSA) had greater success with standard therapy (48.6%) than daptomycin (44.6%), which was also not statistically significant (P=0.76). Nine patients in each group had a final diagnosis of left-sided endocarditis; one patient in the daptomycin group and 2 patients in the standard therapy group had a successful outcome; Therapy failed in all patients with left-sided endocarditis caused by MRSA. Overall rates of failure were similar between groups; however, the reasons for failure differed. Daptomycin failure was more often due to relapsing *S aureus* infection (19 daptomycin vs 11 standard therapy; P=0.17), whereas failure with standard therapy was often related to adverse events leading to discontinuation (17 standard therapy vs 8 daptomycin; P=0.06). Renal dysfunction was noted in 11% of patients in the daptomycin group and 26.3% in the standard therapy group (P=0.004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rehm et al.[88] (2008) Daptomycin 6 mg/kg IV every 24 hours vs vancomycin 1 g IV every 12 h with gentamicin 1 mg/kg IV every 8 hours	RCT, OL, MC Patients with methicillin-resistant *S. aureus* (MRSA) bacteremia or endocarditis	N=89 6 weeks	Primary: Clinical cure rates	Primary: The overall success rate was 44.4% for patients who received daptomycin and 32.6% for patients who received vancomycin/gentamicin (95% CI, -8.3 to 32.1). Success rates for daptomycin vs vancomycin/gentamicin were 45% vs 27% in complicated bacteremia, 60% vs 45% in uncomplicated bacteremia and 50% vs 50% in right-sided MRSA endocarditis. Cure rates in patients with septic emboli and in patients who received pre-enrolment vancomycin were similar between treatment groups. None of the nine patients with left-sided endocarditis was successfully treated. Among patients younger than 75 years of age, 18 of 35 (51.4%) in the daptomycin arm and 14 of 39 (35.8%) in the vancomycin/gentamicin group were judged to have had a successful outcome, but among patients 75 years of age or older, 2 of the 10 receiving daptomycin and none of the 4 in the vancomycin/gentamicin arm were successfully treated. Persisting or relapsing bacteremia occurred in 27% of daptomycin and 21% of vancomycin/gentamicin patients; among these patients, MICs of ≥2 mg/L occurred in five daptomycin and four vancomycin/gentamicin patients.
El-Khoury et al.[50] (2003) Linezolid 600 mg IV/PO BID (<40 kg received 10 mg/kg BID)	OL, MC Solid organ transplant patients with vancomycin-resistant *E faecium*	N=85 Variable duration	Primary: Clinical resolution of infection	Primary: A total of 53 patients (62.4%) survived with linezolid treatment (clinical resolution), whereas death occurred in 32 patients (32.9%). Documented negative cultures post-therapy were obtained in 47 of patients that survived. Mean duration of therapy for cured patients was 23.5 days. Adverse reactions included thrombocytopenia (4 patients), leukocytopenia (3 patients), and increase in blood pressure (1 patient).
Raad et al.[51]	PRO, RCT, OL	N=40	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2004) Linezolid 600 mg every 12 hours vs quinupristin-dalfopristin 7.5 mg/kg every 8 hours	Patients ≥18 years of age with infections caused by vancomycin-resistant *E faecium*	39 months	Safety Secondary: Efficacy	The rate of myalgias/arthralgias in patients receiving quinupristin-dalfopristin was 33% as compared to 0% in patients receiving linezolid (P<0.01). All other reports of adverse effects were found to be not significant (P>0.05). Secondary: Clinical response at the end of therapy were not significantly different between patients receiving quinupristin-dalfopristin and patients receiving linezolid (P=0.6). There was no statistically significant difference between the number of deaths caused by infection, relapse, or microbiological response between the two treatment arms (all P>0.05).
Kohno et al.[93] (2007) Linezolid 600 mg every 12 hours vs vancomycin 1 g every 12 hours	RCT Patients with nosocomial pneumonia, complicated skin and soft-tissue infections or sepsis caused by methicillin-resistant *Staphylococcus aureus* (MRSA)	N=151 7-14 days	Primary: Clinical success rates	Primary: Clinical success rates in the MRSA microbiologically evaluable population were 62.9% and 50.0% for the linezolid and vancomycin groups, respectively (P=NS). Microbiological eradication rates were 79.0% and 30.0% for the linezolid and vancomycin groups, respectively (P<0.0001). At follow-up, the clinical success rates were 36.7% for both groups and the microbiological eradication rates were 46.8% and 36.7%, respectively. Reversible anemia (13%) and thrombocytopenia (19%) were reported more frequently in linezolid patients. Significantly low platelet counts were observed more frequently in patients receiving vancomycin than in linezolid patients (6% vs 3%). Mean changes in hemoglobin levels between the two groups were not different.
Solomkin et al.[128] (2009) Metronidazole 500 mg IV twice daily plus ceftriaxone 2 g IV once daily for	RCT, DB, MC Patients ≥18 years of age with community-origin complicated intra-abdominal	N=364 Up to 28 days	Primary: Clinical success rate at the test-of-cure (TOC) visit (10 to 14 days after the end of therapy)	Primary: At the TOC visit, cure rates were 90.2% for moxifloxacin and 96.5% for ceftriaxone/metronidazole (95% CI, −11.7 to −1.7). In the ITT population, the clinical cure rates were 87.2% for moxifloxacin and 91.2% for ceftriaxone/metronidazole (95% CI, −10.7 to 1.9). Moxifloxacin was found to be non-inferior to ceftriaxone/metronidazole in the PP and ITT populations.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
3 to 14 days vs moxifloxacin 400 mg IV once daily for 3 to 14 days	infections (cIAIs) with an expected duration of treatment with IV antimicrobials of 3-14 days		Secondary: Clinical and bacteriological success rates on days 3 and 5 during treatment and at the end-of-therapy (EOT); bacteriological success rate at the TOC visit; and clinical success rate at the TOC visit in patients with bacteriologically proven cIAI	Secondary: During treatment, clinical improvement occurred in similar proportions of PP patients in the moxifloxacin group (31.0%) and the ceftriaxone/metronidazole group (28.1%). In the ITT population, clinical improvement occurred in 30.6% of patients receiving moxifloxacin and 27.1% of patients receiving ceftriaxone/metronidazole. In the per protocol population, clinical resolution at EOT occurred in 92.5% of patients receiving moxifloxacin and in 97.1% of patients receiving ceftriaxone/metronidazole (95% CI, −9.8 to −0.2). In the ITT population, clinical resolution at EOT occurred in 91.1% of patients receiving moxifloxacin and in 94.5% of patients receiving ceftriaxone/metronidazole. Bacteriological success rates were comparable between treatment groups. The bacteriological success rates in the MBV population at TOC support the clinical results of moxifloxacin vs ceftriaxone/metronidazole (89.4% vs 95.9%, respectively; 95% CI, −13.3 to −0.6). The overall incidence of treatment-emergent AEs was similar between the two treatment groups (31.7% with moxifloxacin vs 24.3% with ceftriaxone/metronidazole; P=0.129).
Towfigh et al.[118] (2010) Metronidazole 1 to 2 g IV daily in divided doses plus ceftriaxone 2 g IV once daily for 4 to 14 days (CTX/MET) vs tigecycline 100 mg	RCT, MC, OL Patients ≥18 years of age with community-origin complicated intra-abdominal infections (cIAIs)	N=473 Up to 35 days	Primary: Clinical response in the clinically evaluable (CE) population at the test-of-cure (TOC) visit Secondary: Bacteriological efficacy and safety	Primary: In the CE population, clinical cure was reported in 70% of patients receiving TGC and in 74% of patients in the CTX/MET group (-4.0; 95% CI, -13.1 to 5.1; P=0.009). TCG was found to be non-inferior to CTX/MET. Secondary: Clinical cure rates for the ME population were 66% with TGC and 70% with CTX/MET (-3.4; 95% CI, -14.5 to 7.8; P=0.020. TCG was found to be non-inferior to CTX/MET. In the c-mITT population, clinical cure was reported in 64% of patients receiving TGC and in 71% of patients receiving CTX/MET (-7.0; 95% CI, -15.8 to 1.08; P=0.038. TGC was found to be non-inferior to CTX/MET.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IV as an initial dose, followed by 50 mg IV every 12 hours for 4 to 14 days (TGC)				*Escherichia coli* and *Bacteroides fragilis* were the most commonly isolated bacteria. For the ME population, clinical cure rates for the different pathogens were similar between the two treatment groups. At TOC in the ME population, infections were cured in 68.0% and 67.0% of all monomicrobial and polymicrobial infections, respectively, in the TGC-treated patients, and 71.5% and 68.3% of all monomicrobial and polymicrobial infections, respectively, in the CTX/MET-treated patients. Adverse events were similar with TGC and CTX/MET. There were no significant differences in the incidence of patients reporting one or more SAEs among the treatment groups (P=1.000). The most frequently reported SAEs overall were abscess (6.6%), infection (1.5%), respiratory failure (1.5%), abdominal pain (1.3%) and ileus (1.3%).
Linden et al.[80] (2001) Quinupristin-dalfopristin 7.5 mg/kg IV every 8 hours	MC, PRO Patients with signs and symptoms of active infection caused by vancomycin-resistant *Enterococcus faecium* (VREF)	N=396 20 days (mean)	Primary: Clinical response rate, bacteriological response rate, overall response rate combined clinical and bacteriological responses	Primary: Clinical response rate was 68.8% in evaluable population; 51% in all-treated population (including indeterminate). Bacteriologic response rate was 68% in evaluable population; 59.8% in all-treated population. Overall response rate was 65.6% in evaluable population; 48.2% in all-treated population. Overall mortality rate in the all-treated group was 28.8% while receiving treatment and 56.6% at 30 days after therapy discontinuation. Arthralgia and myalgia were common adverse events and reasons for therapy discontinuation; however, reversible after treatment discontinuation. A total of 11 patients in the all-treated population experienced superinfection caused by gram-positive pathogens.
Chong et al.[131] (2010) Quinupristin - dalfopristin 7.5 mg/kg IV every 8 hours for ≥48 hours	RETRO Patients ≥16 years of age with vancomycin-resistant *Enterococcus faecium* (VREF)	N=113 Variable duration	Primary: Rates of 30-day mortality, microbiological response, and development of resistance	Primary: The 30-day mortality rate was 48% in patients who received quinupristin-dalfopristin compared to 41% of patients who received linezolid (P=0.45). Microbiological response was observed in 60% of patients receiving quinupristin-dalfopristin compared to 66% of patients receiving linezolid (P=0.51). The development of resistance to quinupristin-dalfopristin in VREF blood

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs linezolid 600 mg IV every 12 hours for ≥48 hours				isolates was observed in 11% of patients for whom follow-up culture data were available. None of the patients developed resistance to linezolid (P=0.02). There were no significant differences in these relapse rates between the treatment groups (P=0.8). Antibiotic-induced thrombocytopenia was observed in 5% of patients in the linezolid group. Platelet counts of all patients recovered after discontinuation of linezolid therapy.
Winston et al.[82] (2000) Quinupristin-dalfopristin, either 7.5 mg/kg IV every 8 hours or 5 mg/kg IV every 8 hours; infused over 60 minutes in 100 mL of D5W through central venous catheter	PRO Hospitalized patients with signs and symptoms of infection confirmed by cultures that are positive for vancomycin-resistant *E faecium* (VREF)	N=24 3 to 36 days	Primary: Clinical responses and bacteriological response	Primary: Eighty-three percent of patients experienced a clinical response (80% of patients given the 7.5 mg/kg dose and 88% of patients given the 5 mg/kg dose. Bacterial eradication occurred in 74% (17/23) of patients. Four patients failed to response to therapy and 4 patients experienced clinical and bacteriologic relapse of VREF 22-67 days after treatment was discontinued. Two patients had persistent VREF. Sixty-nine percent of patients died during hospitalization; 4 due to VREF infection and 12 due to other causes, including liver failure, invasive fungal infection, cardiac failure, *Citrobacter freundii* bacteremia, acute leukemia and fungal infection, pancreatic carcinoma, and graft-versus-host disease. Thirty-three percent of patients experienced arthralgias and myalgias (a higher incidence with the use of high dose [8 patients experienced arthralgias and myalgias with 7.5 mg/kg and none in 5 mg/kg dose]). Six patients experienced superinfection due to *Candida* fungemia, *Enterobacter cloacae* pneumonia, and *Enterococcus faecalis*.
Rehm et al.[81] (2001) Quinupristin-dalfopristin 7.5 mg/kg every 8 or 12 hours diluted in	MC, PRO Patients who participated in clinical trials with quinupristin/ dalfopristin for	N=37 9 days inpatient & 22 days as outpatient (mean)	Primary: Clinical responses, bacteriological response, adverse events	Primary: Overall clinical success rate was 89.2% and bacteriological success rate was also 89.2%. 86.5% completed study without hospital readmission. 5 patients required hospital readmission due to recurrent MRSA, central catheter-related bacteremia, chest pain, elevated liver enzymes, and neutropenic fever.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100 mL (if using central venous catheter) or 240 mL (if using peripheral venous catheter) of D5W; as 1 hour infusion	either emergency use or for assessment of safety and efficacy in Phase III studies and continued to receive quinupristin/ dalfopristin after hospital discharge			Nineteen patients (51.4%) experienced non-venous clinical adverse events (most common: myalgia (18.9%), nausea (18.9%), arthralgia (13.5%), diarrhea, headache, and vomiting). Sixteen patients (43.2%) experienced venous access adverse events (most common: drug infusion pain, local edema, phlebitis). Five (13.5%) patients experienced abnormal lab results (anemia, azotemia, and elevated transaminase).
Heldman et al.[32] (1996) Vancomycin 1 g IV every 12 hours or oxacillin 2 g IV every 4 hours + gentamicin (for first 5 days) vs ciprofloxacin 750 mg PO BID and rifampin 300 mg PO BID Cefazolin was allowed when there was a contraindication to vancomycin.	PRO, RCT, OL Injection drug users (IVDU) with febrile illness meeting criteria for right-sided staphylococcal endocarditis	N=573 Treatment: 28 days Follow-up: 35 days posttreatment	Primary: Cure rate and treatment failure	Primary: There was no statistically significant difference in cure rates (95% with PO therapy, 88% with IV therapy; P=0.6); Information from subjects who did not complete the full 28 day course of treatment showed similar cure rates (90% with oral and 91% with IV; P=0.9) Treatment failures were reported in 3 patients in the parenteral therapy group and 1 in the oral therapy group. Subjects with right-sided endocarditis were predominantly male and African-American. Human immunodeficiency virus (HIV) was present in 68.5% of those with suspected or confirmed right-sided staphylococcal endocarditis. Toxicity was more common with IV therapy vs PO (noted in 1 patient receiving PO [2.8%] vs 24 patients receiving IV [61.5%]; P=0.0007). Nephrotoxicity occurred in 10 patients in the IV arm, vs none in the PO arm (25.6%; P=0.001).
Stevens et al.[54] (2002) Vancomycin 1 g IV QD	MC, OL, RCT Hospitalized/ institutionalized patients with	N=460 7-28 days	Primary: Clinical outcomes and microbiological outcomes	Primary: Clinical cure rate was 73.2% with linezolid vs 73.1% with vancomycin (P=0.99) in evaluable patients with MRSA (N=116) at the TOC visit. There were no differences in clinical response between vancomycin and linezolid for other population subgroups (P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs linezolid 600 mg IV BID Upon clinical improvement, linezolid-treated patients could be changed to linezolid 600 mg PO BID.	methicillin-resistant *S aureus* infections			Microbiological success rate was 58.9% with linezolid vs 63.2% with vancomycin (P=0.65) in evaluable patients with MRSA at the TOC visit. Adverse event rates were similar between groups (P=0.143). A total of 61% of the linezolid group received oral administration.
Shorr et al.[55] (2005) Vancomycin 1 g IV every 12 hours vs linezolid 600 mg IV every 12 hours	MA (PRO, RCT) Patients with *S aureus* bacteremia (pneumonia 48 hours after hospital admission, complicated skin and soft tissue infections, or MRSA infections)	N=144 7-35 days	Primary: Clinical cure of primary infection at end of therapy, microbiological eradication of *S aureus* bacteremia, and overall survival	Primary: In clinically evaluable patients, incidence of cure was 55% (28/51) in patients given linezolid and 52% (25/48) in patients given vancomycin (1.12; 95% CI, 0.51 to 2.47). In the ITT population, clinical cure occurred in 28/74 (38%) patients given linezolid and 25/70 (36%) patients given vancomycin. In patients with MRSA bacteremia, 56% (14/25) of linezolid-treated patients and 46% (13/28) of vancomycin treated patients had a cure (1.47; 95% CI, 0.50 to 4.34). Microbiological success occurred in 69% of linezolid-treated patients and 73% of vancomycin-treated patients (OR, 0.83; 95% CI, 0.37 to 1.87). The survival rate was similar for both treatment groups in patients with MRSA bacteremia as well as overall *S aureus* bacteremia. Mean duration of therapy was shorter with IV linezolid than with vancomycin (8.6 vs 11.7, P=0.004). Linezolid was given IV for >7 days after which it could be switched to PO.
Fortun et al.[33] (2001)	PRO, OL, RCT	N=31	Primary: Cure, clinical	Primary: 11/11 (100%) of patients in the cloxacillin group had a clinical cure

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Vancomycin 500 mg IV every 6 hours vs teicoplanin* 12 mg/kg IV every 24 hours vs cloxacillin 2 g IV every 4 hours Groups received gentamicin 1.5 mg/kg IV every 8 hours.	Parenteral drug users with fever, MSSA, and either septic pulmonary embolism, tricuspid regurgitation murmur, or echocardiographic evidence of endocarditis	30 months	failure microbiological failure, microbiological relapse	compared to 6/10 (60%) in the vancomycin group and 7/10 (70%) in the teicoplanin group; P=0.03. Clinical failure occurred in 30% of the vancomycin group, 10% of the teicoplanin group, and none of the cloxacillin group. No patient experienced microbiological failure. Microbiological relapse occurred with 10% receiving vancomycin, 20% receiving teicoplanin, and no relapse occurred with cloxacillin therapy. Adverse effects occurred in 20% of patients in the vancomycin group, 30% of patients in the teicoplanin group, and none of the patients in the cloxacillin group.

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, PM=at night, QID=four times daily, IM=intramuscular, IV=intravenous, PO=oral
Study abbreviations: CI: confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single-blind, XO=crossover
Miscellaneous abbreviations: CHF=chronic heart failure, EOT=end of therapy, GABHS=group A β-hemolytic streptococcus, CI=confidence interval, HIV=human immunodeficiency virus, ITT=intention to treat or intent to treat, IVDU=intravenous or injectable drug user, LOS=length of hospital stay, MRSA=methicillin-resistant *S aureus*, MSSA=methicillin-susceptible *S aureus*, PaO2=plasma partial oxygen pressure, PCP=*Pneumocystis carinii* pneumonia, PRP=penicillinase-resistant penicillin, TOC=test-of-cure visit, TLUS=the last unformed stool, SMX-TMP=sulfamethoxazole-trimethoprim, BMT-H_2=bismuth subsalicylate, tetracycline and metronidazole with an H_2-receptor antagonist, BMT-PPI=bismuth subsalicylate, tetracycline and metronidazole with a PPI, BTM14=bismuth subcitrate, tetracycline, and metronidazole, MLC=metronidazole, lansoprazole, and clarithromycin, MRSA=methicillin-resistant *Staphylococcus aureus*, PAC7=pantoprazole, amoxicillin, and clarithromycin, PBTM7=pantoprazole, bismuth subcitrate, tetracycline, and metronidazole, PPI=proton-pump inhibitor, UBT=urea breath test

Additional Evidence

Dose Simplification
Carroll et al. evaluated the efficacy of clindamycin administered for 3 doses (short-course) versus 15 doses (long-course) for the prophylaxis of wound infections in patients with head and neck cancer undergoing reconstructive surgery.[67] The incidence of wound infections and other complications was not significantly different among the treatment groups. Livingston et al. compared the efficacy of gentamicin and clindamycin given once daily versus every 8 hours for the treatment of postpartum endometritis.[68] There was no significant different in the treatment success rates among the treatment groups (82% vs 69%, respectively; P=0.12). Cohen et al. evaluated the efficacy of vancomycin administered once-daily versus twice-daily in hospitalized patients.[69] There was no significant difference in clinical response rates among the treatment groups (92.1% vs 94.2%, respectively; P=0.72).

Stable Therapy
McCollum et al. evaluated converting patients from intravenous vancomycin to oral linezolid for the treatment of methicillin-resistant *Staphylococcus* species.[70] Of 177 patients treated with vancomycin, 58% were eligible for conversion to oral therapy with linezolid and 31% were eligible for early hospital discharge with continuation of oral therapy. Early discharge was associated with a decrease in the length of stay by 3.3 days. Li et al. assessed the use of linezolid or vancomycin for the treatment of complicated skin and soft-tissue infections on hospital length of stay.[58] Patients received intravenous linezolid followed by oral linezolid, or monotherapy with intravenous vancomycin for up to 4 weeks. Length of hospital stay was 8 days in the linezolid group compared to 16 days in the vancomycin group (P=0.0025).

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 20. Relative Cost of the Antibacterials, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Bacitracin	injection	Baciim®*	$$$$$	$$$$$
Bismuth subsalicylate, metronidazole, and tetracycline	combination package	Helidac®	$$$$$	N/A
Clindamycin	capsule, injection, solution	Cleocin HCl®*, Cleocin Palmitate®*, Cleocin Phosphate®*, Cleocin Phosphate in D5W®	$$-$$$$$	$-$$$$
Colistimethate	injection	Coly-Mycin M Parenteral®*	$$$$$	$$$$$
Colloidal bismuth subcitrate, metronidazole, and tetracycline	capsule	Pylera®	$$$$$	N/A
Daptomycin	injection	Cubicin®	$$$$$	N/A
Lincomycin	injection	Lincocin®	$$$$$	N/A
Linezolid	injection, suspension, tablet	Zyvox®	$$$$$	N/A
Polymyxin B sulfate	injection	N/A	N/A	$$$$
Quinupristin and dalfopristin	injection	Synercid®	$$$$$	N/A
Rifaximin	tablet	Xifaxan®	$$$$$	N/A
Telavancin	injection	Vibativ®	$$$$$	N/A
Vancomycin	capsule, injection	Vancocin®	$$$$$	$-$$$$$

*Generic is available in at least one dosage form or strength.
N/A=not available

X. Conclusions

The miscellaneous antibacterials are a diverse group of products that are used to treat many different types of infections.[1-17] The FDA-approved indications vary depending on the particular agent and antimicrobial properties. It is important to analyze current treatment guidelines and published studies when making therapeutic decisions about the miscellaneous antibacterial agents. Bacitracin, clindamycin, colistimethate, polymyxin B sulfate and vancomycin are available in a generic formulation.

The use of bacitracin is limited to the treatment of infants with pneumonia and empyema caused by susceptible strains of staphylococci. Treatment may cause renal failure due to tubular and glomerular necrosis; therefore, renal function should be carefully determined prior to and daily during therapy. The concurrent use of other nephrotoxic drugs should be avoided. Polymyxin B sulfate and colistimethate are approved for the treatment of serious infections caused by susceptible gram-negative bacteria when less toxic drugs are ineffective or contraindicated. The use of these agents has resulted in nephrotoxicity and neurotoxicity. Guidelines do not discuss the use of bacitracin, polymyxin B sulfate or colistimethate and published clinical trials are limited.

The lincosamide antibacterials include clindamycin and lincomycin. Guidelines recommended the use of clindamycin for the treatment of skin and soft-tissue infections and pelvic inflammatory disease.[20-21,29] Lincomycin is not discussed in the available guidelines and has no therapeutic advantage over clindamycin. Although there are many FDA-approved indications for clindamycin, the increased risk of *Clostridium difficile*-associated diarrhea (which may end fatally) limits the use of this agent. The lincosamides should be reserved for the treatment of serious infections for which less toxic antimicrobial agents are inappropriate.[1]

Daptomycin is approved for the treatment of complicated skin and skin-structure infections, *Staphylococcus aureus* bacteremia, and right-sided infective endocarditis. The spectrum of activity with daptomycin is similar to that of vancomycin. Guidelines recommend daptomycin as one of several options for the initial treatment of soft-tissue infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA).[20] Published studies have demonstrated similar clinical response rates when daptomycin was compared to vancomycin or penicillinase-resistant penicillins.[31,56,87-88]

Linezolid is approved for the treatment of skin and skin-structure infections, pneumonia and vancomycin-resistant *Enterococcus faecium* (VRE) infections. Guidelines recommend the use of linezolid as an initial treatment option for endocarditis (due to VRE), meningitis (due to MRSA and VRE), skin and soft-tissue infections (due to MRSA), diabetic foot infections, as well as community-acquired and nosocomial pneumonia (due to MRSA).[20-21,27-28,65,97,132,136] Several trials have demonstrated similar clinical response rates when linezolid was compared to vancomycin.[42-43,45,54-55,57,65,91,93,129] Linezolid can be administered either orally or parenterally when treating serious infections. Vancomycin is also available in an oral and injectable formulation; however, oral vancomycin has only been shown to be effective for the treatment of enterocolitis and *Clostridium difficile*-associated diarrhea. The intravenous formulation must be used for the treatment of serious infections caused by staphylococci, including methicillin-resistant strains. Studies have demonstrated a shorter length of hospital stay and duration of intravenous therapy with the use of linezolid compared to vancomycin.[58-60] Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy.[13]

Quinupristin/dalfopristin is approved for the treatment of complicated skin and skin-structure infections.[14] In November 2010, the FDA removed the indication for the treatment of vancomycin-resistant *Enterococcus faecium* because data failed to verify clinical benefit.[14,145] Guidelines recommend the use of quinupristin/dalfopristin as one of several options for the treatment of skin and soft-tissue infections (due to MRSA) and endocarditis (due to VRE).[20,28] Studies have demonstrated similar clinical response rates when quinupristin/dalfopristin was compared to cefazolin, linezolid, oxacillin and vancomycin.[46,51,63,83]

Telavancin is approved for the treatment of complicated skin and skin-structure infections (SSTIs) caused by susceptible gram-positive bacteria (including MRSA).[16] For hospitalized patients with complicated SSTIs, empirical therapy for MRSA should be considered.[136] Treatment options include telavancin, vancomycin, linezolid, daptomycin, and clindamycin. Two studies compared telavancin to standard therapy (penicillinase-resistant penicillin or vancomycin) in patients with complicated SSTIs caused by gram-positive organisms.[124-126] Cure rates were similar among the treatment groups, including in patients with MRSA at baseline. Telavancin was also compared to vancomycin in patients with hospital-acquired pneumonia due to gram-positive organisms.[127] Cure rates were similar among the treatment groups, including in patients with MRSA at baseline. Increases in serum creatinine (up to 1.5 times baseline) have occurred more frequently in patients receiving telavancin (15%) compared to patients receiving vancomycin (7%).[16] Renal function should be monitored in patients receiving telavancin prior to the start of therapy, during treatment, and at the end of therapy.

Intravenous vancomycin is approved for the treatment of serious infections caused by susceptible strains of methicillin-resistant staphylococci, for penicillin-allergic patients, for patients who cannot receive or who have failed to respond to other drugs, and for infections caused by vancomycin-susceptible organisms that are resistant to other antimicrobial drugs.[17] Vancomycin is also effective for the treatment of staphylococcal endocarditis, septicemia, bone infections, lower respiratory tract infections, as well as skin and skin-structure infections. As discussed previously, several studies have demonstrated similar clinical response rates when vancomycin was compared to daptomycin, linezolid, and quinupristin/dalfopristin.[31,42-46,54-57,83,87-88,91,93] Ototoxicity and nephrotoxicity have been reported with the use of intravenous vancomycin.[17] Ototoxicity may be transient or permanent and has been reported mostly in patients who have been given excessive doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Vancomycin should be used with caution in patients with renal insufficiency because the risk of toxicity is appreciably increased by high, prolonged blood concentrations.

Rifaximin is approved for the treatment of travelers' diarrhea and to reduce the risk of overt hepatic encephalopathy recurrence.[15] For travelers' diarrhea, guidelines recommend empirical treatment with one of several antibiotics, including quinolones, azithromycin, sulfamethoxazole-trimethoprim and rifaximin.[26,135] Studies have demonstrated similar efficacy when rifaximin was compared to sulfamethoxazole-trimethoprim and ciprofloxacin.[65-66,99] For the treatment of hepatic encephalopathy, guidelines recommend lactulose as initial therapy.[144] Antibiotics are considered an alternative treatment option for acute and chronic encephalopathy. Clinical trials have evaluated the short-term use of rifaximin for the treatment of acute hepatic encephalopathy.[101-

[109] Rifaximin was found to be as effective, or more effective, than lactulose and neomycin.[102-103,106-108] Bass et al. evaluated the long-term efficacy and safety of rifaximin in patients who were in remission from hepatic encephalopathy.[100] Over a 6-month period, breakthrough episodes of hepatic encephalopathy were reported in 22% of patients receiving rifaximin compared to 46% of patients receiving placebo (P<0.001). Hospitalizations occurred in 14% of patients receiving rifaximin and in 23% of patients receiving placebo (P=0.01). This study did not directly compare rifaximin to other standard treatments for hepatic encephalopathy. Lactulose was used concomitantly by 91% of the patients in both treatment arms.

There are two combination products containing bismuth, metronidazole and tetracycline that are included in this review (Helidac® and Pylera®). Both products are used to eradicate *Helicobacter pylori* in patients with duodenal ulcer disease. Helidac® is supplied in a 14-day blister card which contains each of the three antibacterial components as separate dosage forms. It should be used in combination with an H_2-receptor antagonist for the treatment of *H. pylori* infections. Pylera® contains all three of the antibacterial components in a single capsule. It should be used in combination with omeprazole for the treatment of *H. pylori* infections. Guidelines recommend either proton-pump inhibitor (PPI)-based triple therapy or quadruple therapy (PPI or H_2-receptor antagonist, bismuth, tetracycline, and metronidazole) for the eradication of *H. pylori*.[22-23] Several clinical trials comparing quadruple therapy to triple therapy have demonstrated comparable efficacy, although this has not been consistently demonstrated.[22-23,71,75,78,85,120,123] There were no published studies found that directly compared Helidac® or Pylera® combination products with bismuth, metronidazole and tetracycline administered as separate formulations.

There is insufficient evidence to support that one brand miscellaneous antibacterial is safer or more efficacious than another within its given indication. Since the majority of these agents are not indicated as first-line therapy for the management of common infectious diseases that would be seen in general use and due to concerns for the development of resistance, these agents should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous antibacterials within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous antibacterial is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2011. Available from Wolters Kluwer Health, Inc. Accessed September 2011.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2011; September 2011.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed September 2011.
4. Baciim® [package insert]. Northport, NY: X-Gen Pharmaceuticals, Inc.; December 2003.
5. Helidac® [package insert]. San Diego, CA: Prometheus Laboratories, Inc.; November 2009.
6. Cleocin HCl® [package insert]. New York, NY: Pfizer, Inc.; June 2011.
7. Cleocin Pediatric® [package insert]. New York, NY: Pfizer, Inc.; January 2008.
8. Cleocin Phosphate® [package insert]. New York, NY: Pfizer, Inc.; June 2011.
9. Coly-Mycin® [package insert]. Rochester, MI: JHP Pharmaceuticals; February 2011.
10. Pylera [package insert]. Birmingham, AL: Axcan Pharma US, Inc; January 2011.
11. Cubicin® [package insert]. Lexington, MA: Cubist Pharmaceuticals; November 2010.
12. Lincocin® [package insert]. New York, NY: Pfizer, Inc.; June 2007.
13. Zyvox® [package insert]. New York, NY: Pharmacia & Upjohn Company; June 2010.
14. Synercid® [package insert]. Bristol, TN: Monarch Pharmaceuticals; August 2010.
15. Xifaxan® [package insert]. Morrisville, NC: Salix Pharmaceuticals, Inc; November 2010.
16. Vibativ® [package insert]. Deerfield, IL: Astellas Pharma US, Inc.; September 2009.
17. Vancocin® HCl Capsules [package insert]. Exton, PA: ViroPharma Incorporated; October 2005.
18. Mandell GL, Bennett JE, Dolin R. Principles and Practices of Infectious Diseases. 6th ed. Vol 1. Philadelphia, PA: Elsevier, Inc.; 2005.
19. American Thoracic Society and the Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388–416.
20. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005 Nov 15;41(10):1373-406.
21. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, LeFrock JL, Lew DP, Mader JT, Norden C, Tan JS; Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004 Oct 1;39(7):885-910.
22. Chey W, Wong B. American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection. Am J Gastroenterol 2007; 102:1808-1825.
23. Hunt R, Fallone C, Veldhuyzan van Zanten S, Sherman P, et al., CHSG 2004 participants. Canadian Helicobacter Study Group Consensus Conference: Update on the management of *Helicobacter pylori*--an evidence-based evaluation of six topics relevant to clinical outcomes in patients evaluated for *H pylori* infection. Can J Gastroenterol. 2004; 18(9):547-554.
24. Malfertheiner P, Megraud F, O'Morain C., et al. Current Concepts in the Management of *Helicobacter pylori* Infection. The Maastricht 2-2000 Consensus Report. European *Helicobacter Pylori* Study Group. Aliment Pharmacol Ther 2002; 16:167-180.
25. Veldhuyzen van Zanten SJ, Flook N, Chiba N, Armstrong D, An evidence-based approach to the management of uninvestigated dyspepsia in the era of *Helicobacter pylori*. Canadian Dyspepsia Working Group. CMAJ. 2000; 162(suppl 12):S3-23.
26. Hill DR, Ericsson CD, Pearson RD, Keystone JS, Freedman DO, Kozarsky PE, et al. The practice of travel medicine: Guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006; 43:1499-1539.
27. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-S72.
28. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. Circulation. Jun 2005;111:e394-e434.
29. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1-110.

30. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50:133-64.
31. Fowler VG, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by staphylococcus aureus. N Eng J Med. 2006;355:653-65.
32. Heldman AW, Hartert TV, Ray SC, Daoud EG, Kowalski TE, Pompili VJ, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med. 1996;101(1):68-76.
33. Fortun J, Navas E, Martinex-Beltran J, et al. Short-course therapy for right-side endocarditis due to Staphylococcus aureus in drug abusers: cloxacillin versus glycopeptides in combination with gentamicin. Clin Infect Dis. 2001;33:120-5.
34. French LM, Smaill FM. Antibiotic regimens for endometritis after delivery. Cochrane Database Syst Rev. 2004;18(4):CD001067.
35. Ugwumadu A, Manyonda I, Reid F, Hay P. Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomized controlled trial. Lancet. 2003;361(9362): 983-8.
36. Arredondo JL, Diaz V, Gaitan H, et al. Oral clindamycin and ciprofloxacin versus intramuscular ceftriaxone and oral doxycycline in the treatment of mild-to-moderate pelvic inflammatory disease in outpatients. Clin Infect Dis. 1997;24(2):170-8.
37. Blanco JD, Gibbs RS, Duff P, Castaneda YS, St Clair PJ. Randomized comparison of ceftazidime versus clindamycin-tobramycin in the treatment of obstetrical and gynecological infections. Antimicrob Agents Chemother. 1983;24(4):500-4.
38. Mahakit CP, Vicente JG, Butt DI, Angeli G, Bansal S, Zambrano DZ. Oral clindamycin 200 mg BID compared with oral amoxicillin/clavulanic acid 1 g BID in the outpatient treatment of acute recurrent pharyngotonsillitis caused by group A beta-hemolytic streptococci: an international, multicenter, randomized, investigator-blinded, prospective trial in patients between ages of 12 and 60 years. Clin Ther. 2006;28(1):99-109.
39. Toma E, Thorne A, Singer J, and CTN-PCP Study Group. Clindamycin with primaquine vs trimethoprim-sulfamethoxazole therapy for mild and moderately severe Pneumocystis carinii pneumonia in patients with AIDS: a multicenter, double-blind, randomized trial (CTN 004). Clin Infect Dis. 1998;27(3):524-30.
40. Allewelt M, Schuler P, Bolcskei PL, et al. Ampicillin + sulbactam vs clindamycin ± cephalosporin for the treatment of aspiration pneumonia and primary lung abscess. Clin Microbiol Infect. 2004;10(2):163-70.
41. Raad I, Hachem R, Hanna H, et al. Treatment of nosocomial postoperative pneumonia in cancer patients: a prospective randomized study. Ann Surg Oncol. 2001;8(2):179-86.
42. Rubinstein E, Cammarata S, Oliphant T, Wunderink R, Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. Clin Infect Dis. 2001;32(3):402-12.
43. Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. Clin Ther. 2003;25(3):980-92.
44. San Pedro GS, Cammarata SK, Oliphant TH, Todisco T, Linezolid Community-Acquired Pneumonia Study Group. Linezolid versus ceftriaxone/cefpodoxime in patients hospitalized for the treatment of streptococcus pneumoniae pneumonia. Scan J Infect Dis. 2002;34(10):720-8.
45. Kaplan SL, Deville JG, Yogev R, Linezolid Pediatric Study Group. Linezolid versus vancomycin for treatment of resistant gram-positive infections in children. Pediatr Infect Dis J. 2003;22(8):677-86.
46. Fagon JY, Patrick DW, Haas A, Nosocomial Pneumonia Group. Treatment of gram-positive nosocomial pneumonia: prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Am J Respir Crit Care Med. 2000;161:753-62.
47. Peltola H, Unkila-Kallio L, Kallio MJ. Simplified treatment of acute staphylococcal osteomyelitis of childhood. Pediatrics. 1997;99:846-50.
48. Linden PK, Kusne S, Coley K, Fontes P, Kramer DJ, Paterson D. Use of parenteral colistin for the treatment of serious infection due to antimicrobial-resistant Pseudomonas aeruginosa. Clin Infect Dis. 2003;37(11):e154-60.
49. Kasakou SK, Michalopoulos A, Soteriades ES, Samonis G, Sermaides GJ, Falagas ME. Combination therapy with intravenous colistin for management of infections due to multidrug-resistant gram-negative bacteria in patients without cystic fibrosis. Antimicrob Agents Chemother. 2005;49(8):3136-46.

50. El-Khoury J, Fishman JA. Linezolid in the treatment of vancomycin-resistant Enterococcus faecium in solid organ transplant recipients: report of a multicenter compassionate-use trial. Transpl Infect Dis. 2003;5(3):121-5.
51. Raad I, Hachem R, Hanna H, et al. Prospective, randomized study comparing quinupristin-dalfopristin with linezolid in the treatment of vancomycin-resistant Enterococcus faecium infections. J Antimicrob Chemother. 2004;53(4):646-9.
52. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. Am J Gastroenterol. 2002;97(7):1769-75.
53. Bricker E, Gard E, Nelson R, Loza A, Novak T, Hansen J. Antibiotic treatment for *clostridium difficile*-associated diarrhea in adults. Cochrane Database Syst Rev. 2005;25(1):CD004610.
54. Stevens DL, Herr D, Lampiris H, Linezolid MRSA Study Group. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. Clin Infect Dis. 2002;34:1481-90.
55. Shorr AF, Kunkel MJ, Kollef M. Linezolid versus vancomycin for *Staphylococcus aureus* bacteraemia: pooled analysis of randomized studies. J Antimicrob Chemother.2005;56:923-9.
56. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI, Daptomycin 98-01 and 99-01 Investigators. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis. 2004;38(12):1673-81.
57. Yogev R, Patterson LE, Kaplan SL, et al. Linezolid for the treatment of complicated skin and skin structure infections in children. Pediatr Infect Dis J. 2003;22(9 Suppl):S172-7.
58. Li JZ, Willke RJ, Rittenhouse BE, Rybak MJ. Effect of linezolid versus vancomycin on length of hospital stay inpatients with complicated skin and soft tissue infections caused by known or suspected methicillin-resistant staphylococci: results from a randomized clinical trial. Surg Infect (Larchmt). 2003;4(1):57-70.
59. Itani KM, Weigelt J, Li JZM Duttagupta S. Linezolid reduces length of stay and duration of intravenous treatment compared with vancomycin for complicated skin and soft tissue infections due to suspected or proven methicillin-resistant *Staphylococcus aureus* (MRSA). Int J Antimicrob Agents.2005;26(6):442-8.
60. Sharpe JN, Shivley EH, Polk HC. Clinical and economic outcomes of oral linezolid versus intravenous vancomycin in the treatment of MRSA-complicated, lower-extremity skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus. Am J Surg.2005;189(4):425-8.
61. Lipsky BA, Itani K, Norden C, Linezolid Diabetic Food Infections Study Group. Treating foot infections in diabetic patients: a randomized, multicenter, open-label trial of linezolid versus ampicillin-sulbactam/amoxicillin-clavulanate. Clin Infect Dis. 2004;38(1):17-24.
62. Stevens DL, Smith LG, Bruss JB. Randomized comparison of linezolid (PNU-100766) versus oxacillin-dicloxacillin for treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother. 2000;44(12):408-13.
63. Nichols RL, Graham DR, Barriere SL, Rodgers A, Wilson SE, Zervos M, et al. Treatment of hospitalized patients with complicated gram-positive skin and skin infections: two randomized, multicentre studies of quinupristin/dalfopristin versus cefazolin, oxacillin or vancomycin. J Antimicrob Chemother. 1999;44:263-73.
64. Steffen R, Sack DA, Riopel L, Jiang Z, Sturchler M, Ericsson, et al. Therapy of travelers' diarrhea with rifaximin on various continents. Am J Gastroenterol.2003;98(5):1073-8.
65. DuPont HL, Ericsson CD, Mathewson JJ, Palazzini E, DuPont MW, Jiang ZD, et al. Rifaximin: a nonabsorbed antimicrobial in the therapy of travelers' diarrhea. Digestion.1998;59:708-14.
66. DuPont HL, Jiang Z, Ericsson CD, Adachi JA, Mathewson JJ, DuPont MW, et al. Rifaximin versus ciprofloxacin for the treatment of travelers' diarrhea: a randomized, double-blind clinical trial. Clin Infect Dis.2001;33:1807-15.
67. Carroll WR, Rosenstiel D, Fix JR, et al. Three-dose vs extended-course clindamycin prophylaxis for free-flap reconstruction of the head and neck. Arch Otolaryngol Head Neck Surg. 2003;129(7):771-4.
68. Livingston JC, Llata E, Rinehart E, et al. Gentamicin and clindamycin therapy in postpartum endometritis: the efficacy of daily dosing versus dosing every 8 hours. Am J Obstet Gynecol. 2003;188(1):146-52.
69. Cohen E, Dadashev A, Drucker M, Samra Z, Rubinstein E, Garty M. Once-daily versus twice-daily intravenous administration of vancomycin for infections in hospitalized patients. J Antimicrob Chemother. 2002;49:155-60.
70. McCollum M, Rhew DC, Parodi S. Cost analysis of switching from IV vancomycin to PO linezolid for the management of methicillin-resistant Staphylococcus species. Clin Ther 2003 Dec;25(12):3173-89.
71. Magaret N, Burm M, Faigel D, Kelly C, Peterson W, Fennerty MB. A randomized trial of lansoprazole, amoxicillin, and clarithromycin versus lansoprazole, bismuth, metronidazole and tetracycline in the retreatment of patients failing initial *Helicobacter pylori* therapy. Dig Dis. 2001;19:174-8.

72. Miehlk S, Kirsch C, Schneider-Brachert W, Haferland C, Neumeyer M, Bästein E, et al. A prospective, randomized study of quadruple therapy and high dose dual therapy for treatment of *Helicobacter pylori* resistant to both metronidazole and clarithromycin. Helicobacter. 2003;8(4):310-9.
73. Altintas E, Ulu O, Sezgin O, Aydin O, Camdeviren H. Comparison of ranitidine bismuth citrate, tetracycline and metronidazole with ranitidine bismuth citrate and azithromycin for the eradication of *Helicobacter pylori* in patients resistant to PPI based triple therapy. Turk J Gastroenterol. 2004;15(2):90-3.
74. Laine L, Estrada R, Trujillo M, Emami S. Randomized comparison of ranitidine bismuth citrate-based triple therapies for *Helicobacter pylori*. Am J Gastroenterol. 1997;92(12):2213-5.
75. Katelaris PH, Forbes GM, Talley NJ, Crotty B. A randomized comparison of quadruple and triple therapies for *Helicobacter pylori* eradication: The QUADRATE study. Gastroenterology. 2002;123(6):1763-9.
76. Kearney DJ, Brousal A. Treatment of *Helicobacter pylori* infection in clinical practice in the United States. Dig Dis Sci. 2000;45(2):2765-71.
77. Saad RJ, Schoenfeld P, Kim HM, Chey WD. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent *Helicobacter pylori* infection: a meta-analysis. Am J Gastroenterol. 2006;101(3):488-96.
78. Perri F, Festa V, Clemente R, Villani MR, Quitadamo M, Caruso N, et al. Randomized study of two rescue therapies for *Helicobacter pylori*-infected patients after failure of standard triple therapies. Am J Gastroenterol. 2001;96(1):58-62.
79. de Boer WA, Haeck PWE, Otten MH, Mulder CJJ. Optimal treatment of *Helicobacter pylori* with ranitidine bismuth citrate (RBC): a randomized comparison between two 7-day triple therapies and a 14-day dual therapy. Am J Gastroenterol. 1998;93(7):1101-7.
80. Linden PK, Moellering Jr RC, Wood CA, Rehm SJ, Flaherty J, Bompart F, Talbot GH. Treatment of Vancomycin-resistant *Enterococcus faecium* infections with quinupristin/dalfopristin. Clin Infect Dis. 2001;33(11):1816-23.
81. Rehm SJ, Graham DR, Srinath L, Prokocimer P, Richard MP, Talbot GH. Successful administration of quinupristin/dalfopristin in the outpatient setting. J Antimicrob Chemother. 2001;47(5):639-45.
82. Winston DJ, Emmanouilides C, Kroeber A, Hindler J, Bruckner DA, Territo MC, et al. Qunupristin/dalfopristin therapy for infections due to vancomycin-resistant enterococcus faecium. Clin Infect Dis. 2000; 30:790-7.
83. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011;364:22-32.
84. Loeffler AM, Drew RH, Perfect JR, Grethe NI, Stephens JW, Gray SL, et al. Safety and efficacy of quinupristin/dalfopristin for treatment of invasive gram-positive infections in pediatric patients. Pediatr Infect Dis J. 2002;21:950-,6.
85. Uygun A, Kadayifci A, Safali M, et al.The efficacy of bismuth containing quadruple therapy as a first-line treatment option for *Helicobacter pylori*. J Dig Dis 2007;8:211-5.
86. Rush D, Abdel-Haq N, Zhu J, et al. Clindamycin versus Unasyn in the treatment of facial cellulitis of odontogenic origin in children. Clin Pediatr (Phila) 2007;46:154-9.
87. Pertel P, Eisenstein B, Link A, et al. The efficacy and safety of daptomycin vs vancomycin for the treatment of cellulitis and erysipelas. Int J Clin Pract 2009;63:368-75.
88. Rehm S, Boucher H, Levine D, et al. Daptomycin versus vancomycin plus gentamicin for treatment of bacteraemia and endocarditis due to Staphylococcus aureus: subset analysis of patients infected with methicillin-resistant isolates. J Antimicrob Chemother. 2008 Dec;62(6):1413-21.
89. Davis S, McKinnon P, Hall L, et al. Daptomycin versus vancomycin for complicated skin and skin structure infections: clinical and economic outcomes. Pharmacotherapy 2007;27:1611-8.
90. Wilcox M, Tack K, Bouza E, et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study. Clin Infect Dis 2009;48:203-12.
91. Wunderink R, Mendelson M, Somero M, et al. Early microbiological response to linezolid vs vancomycin in ventilator-associated pneumonia due to methicillin-resistant Staphylococcus aureus. Chest 2008;134:1200-7.
92. Falagas M, Siempos I, Vardakas K, et al. Linezolid versus glycopeptide or beta-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomised controlled trials. Lancet Infect Dis 2008;8:53-66.
93. Kohno S, Yamaguchi K, Aikawa N, et al. Linezolid versus vancomycin for the treatment of infections caused by methicillin-resistant Staphylococcus aureus in Japan. J Antimicrob Chemother 2007;60:1361-9.
94. Dupont H, Jiang Z, Belkind-Gerson J, et al. Treatment of travelers' diarrhea: randomized trial comparing rifaximin, rifaximin plus loperamide, and loperamide alone. Clin Gastroenterol Hepatol 2007;5:451-6.

95. Zar F, Bakkanagari S, Moorthi K, et al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007 Aug 1;45(3):302-7.
96. Nelson R. Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD004610.
97. DuPont HL, Jiang ZD, Okhuysen PC, et al. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. Ann Intern Med 2005;142:805-12.
98. Martinez-Sandoval F, Ericsson CD, Jiang ZD, et al. Prevention of travelers' diarrhea with rifaximin in US travelers to Mexico. J Travel Med 2010;17:111-7.
99. Taylor DN, Bourgeois AL, Ericsson CD, et al. A randomized, double-blind, multicenter study of rifaximin compared with placebo and with ciprofloxacin in the treatment of travelers' diarrhea. Am J Trop Med Hyg 2006;74:1060-6.
100. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010; 362:1071-1081.
101. Williams R, James OF, Warnes TW, et al. Evaluation of the efficacy and safety of rifaximin in the treatment of hepatic encephalopathy: a double-blind, randomized, dose-finding multi-centre study. Eur J Gastroenterol Hepatol 2000;12(2): 203–8.
102. Bucci L, Palmieri GC. Double-blind, double-dummy comparison between treatment with rifaximin and lactulose in patients with medium to severe degree hepatic encephalopathy. Curr Med Res Opin 1993;13(2):109–18.
103. Paik YH, Lee KS, Han KH, et al. Comparison of rifaximin and lactulose for the treatment of hepatic encephalopathy: a prospective randomized study. Yonsei Med J 2005;46:399-407.
104. Neff GW, Kemmer N, Zacharias VC, et al. Analysis of hospitalizations comparing rifaximin versus lactulose in the management of hepatic encephalopathy. Transplant Proc 2006; 38:3552-5.
105. Leevy CB, Phillips JA. Hospitalizations during the use of rifaximin versus lactulose for the treatment of hepatic encephalopathy. Dig Dis Sci 2007;52:737-41.
106. Mas A, Rodés J, Sunyer L, et al. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blind, double-dummy, controlled clinical trial. J Hepatol 2003;38:51-8.
107. Jiang Q, Jiang XH, Zheng MH, et al. Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis. Eur J Gastroenterol Hepatol 2008;20:1064-70.
108. Festi D, Mazzella G, Orsini M. Rifaximin in the treatment of chronic hepatic encephalopathy: results of a multicenter study of efficacy and safety. Curr Ther Res 1993;54(5):598–609.
109. Miglio F, Valpiani D, Rossellini SR, et al. Rifaximin, a nonabsorbable rifamycin, for the treatment of hepatic encephalopathy. A double-blind, randomised trial. Curr Med Res Opin 1997;13(10):593–601.
110. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 2011;364:422-31.
111. Corey GR, Wilcox MH, Talbot GH, et al. CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65 Suppl 4:iv41-51.
112. Wilcox MH, Corey GR, Talbot GH, et al. CANVAS 2: the second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65 Suppl 4:iv53-iv65.
113. Corey GR, Wilcox M, Talbot GH, et al. Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. Clin Infect Dis 2010;51:641-50.
114. Chen AE, Carroll KC, Diener-West M, et al. Randomized controlled trial of cephalexin versus clindamycin for uncomplicated pediatric skin infections. Pediatrics 2011;127:e573-80.
115. Sidhu SS, Goyal O, Mishra BP, et al. Rifaximin improves psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy (the RIME Trial). Am J Gastroenterol 2011;106:307-16.
116. Khawcharoenporn T, Tice A. Empiric outpatient therapy with trimethoprim-sulfamethoxazole, cephalexin, or clindamycin for cellulitis. Am J Med 2010;123:942-50.
117. Chuang YC, Chang CM, Aradhya S, et al. Efficacy and safety of tigecycline monotherapy compared with vancomycin-aztreonam in the treatment of complicated skin and skin structure infections in patients from India and Taiwan. J Microbiol Immunol Infect 2011;44:116-24.

118. Towfigh S, Pasternak J, Poirier A, et al. A multicentre, open-label, randomized comparative study of tigecycline versus ceftriaxone sodium plus metronidazole for the treatment of hospitalized subjects with complicated intra-abdominal infections. Clin Microbiol Infect 2010;16:1274-81.
119. Zheng Q, Chen WJ, Lu H, et al. Comparison of the efficacy of triple versus quadruple therapy on the eradication of *Helicobacter pylori* and antibiotic resistance. J Dig Dis 2010;11:313-8.
120. Luther J, Higgins PD, Schoenfeld PS, et al. Empiric quadruple vs triple therapy for primary treatment of *Helicobacter pylori* infection: Systematic review and meta-analysis of efficacy and tolerability. Am J Gastroenterol 2010;105:65-73.
121. Malfertheiner P, Bazzoli F, Delchier JC, et al. *Helicobacter pylori* eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. Lancet 2011;377:905-13.
122. Wu DC, Hsu PI, Tseng HH, et al. *Helicobacter pylori* infection: a randomized, controlled study comparing 2 rescue therapies after failure of standard triple therapies. Medicine (Baltimore) 2011;90:180-5.
123. Songür Y, Senol A, Balkarli A, et al. Triple or quadruple tetracycline-based therapies versus standard triple treatment for *Helicobacter pylori* treatment. Am J Med Sci 2009;338:50-3.
124. Stryjewski ME, O'Riordan WD, Lau WK, et al. Telavancin versus standard therapy for treatment of complicated skin and soft-tissue infections due to gram-positive bacteria. Clin Infect Dis 2005;40:1601-7.
125. Stryjewski ME, Chu VH, O'Riordan WD, et al. Telavancin versus standard therapy for treatment of complicated skin and skin structure infections caused by gram-positive bacteria: FAST 2 study. Antimicrob Agents Chemother 2006;50:862-7.
126. Stryjewski ME, Graham DR, Wilson SE, et al. Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections caused by gram-positive organisms. Clin Infect Dis 2008;46:1683-93.
127. Rubinstein E, Lalani T, Corey GR, et al. Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. Clin Infect Dis 2011;52:31-40.
128. Solomkin J, Zhao YP, Ma EL, et al. Moxifloxacin is non-inferior to combination therapy with ceftriaxone plus metronidazole in patients with community-origin complicated intra-abdominal infections. Int J Antimicrob Agents 2009;34:439-45.
129. Itani KM, Dryden MS, Bhattacharyya H, et al. Efficacy and safety of linezolid versus vancomycin for the treatment of complicated skin and soft-tissue infections proven to be caused by methicillin-resistant *Staphylococcus aureus*. Am J Surg 2010;199:804-16.
130. Musher DM, Logan N, Bressler AM, et al. Nitazoxanide versus vancomycin in *Clostridium difficile* infection: a randomized, double-blind study. Clin Infect Dis 2009;48:e41-6.
131. Chong YP, Lee SO, Song EH, et al. Quinupristin-dalfopristin versus linezolid for the treatment of vancomycin-resistant *Enterococcus faecium* bacteraemia: efficacy and development of resistance. Scand J Infect Dis 2010;42:491-9.
132. Chaudhuri A, Martinez-Martin P, Kennedy PG, Andrew Seaton R, Portegies P, Bojar M, Steiner I; EFNS Task Force. EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. Eur J Neurol 2008;15:649-59.
133. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol 2010;31:431-55.
134. Bauer MP, Kuijper EJ, van Dissel JT, European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for *Clostridium difficile* infection (CDI). Clin Microbiol Infect 2009;15:1067-79.
135. World Gastroenterology Organization (WGO). WGO practice guideline: acute diarrhea. Munich, Germany: World Gastroenterology Organization (WGO); 2008 Mar. 28 p. http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/01_acute_diarrhea.pdf. Accessed December 2011.
136. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, Rybak MJ, Talan DA, Chambers HF. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant staphylococcus aureus infections in adults and children. Clin Infect Dis 2011 Feb;52:1-38.
137. Bonow R, Carabello B, Chatterjee K et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College

of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e1-142.

138. American Academy of Pediatrics subcommittee on the management of sinusitis and committee on quality improvement. Clinical practice guideline: management of sinusitis. Pediatrics. 2001;108(3):798-808.
139. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011;53:e25-76.
140. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009;58(RR-4):1-207.
141. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis. 2004;38:1706–15.
142. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Eur Heart J 2009;30:2369-413.
143. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR, Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:e56-93
144. American College of Gastroenterology. Practice guidelines: hepatic encephalopathy. Am J Gastroenterology 2001;96:1968-1976.
145. Food and Drug Administration. Communication on supplemental approval. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/050747s011,050748s009,050748s010ltr.pdf. Accessed December 2011.