Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
May 9, 2012

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Pharmacotherapy Class Reviews

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Allylamines
AHFS Class 081404
May 9, 2012

I. Overview

Serious fungal infections are relatively rare, but in recent years they have taken on greater importance in clinical practice because of an increased number of opportunistic fungal infections in immunocompromised patients. Contributing factors have been the advent of human immunodeficiency virus (HIV) and the more frequent use of immunosuppressive drugs as part of other therapies. For instance, hematopoietic or solid-organ transplant patients, or those undergoing chemotherapy for hematologic malignancies, are potential hosts for systemic fungal invasion.[6] Fungal infections can also be brought on by antibiotic use, particularly with broad-spectrum antibiotics which kill organisms that inhibit fungal growth, or with the use of antibiotics for long-term prophylaxis.[6]

The systemic antifungals are categorized into 6 different AHFS classes, including allylamines, azoles, echinocandins, polyenes, pyrimidines and miscellaneous agents. The agents which make up these classes differ in their structure, pharmacokinetics, spectrum of activity and FDA-approved indications.

Terbinafine is the only allylamine currently available and it is approved for the treatment of onychomycosis and tinea capitis.[1-5] It inhibits biosynthesis of ergosterol via inhibition of squalene epoxidase enzyme. This results in fungal cell death, which is primarily due to increased membrane permeability.

The allylamines that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The topical antifungals were previously reviewed with the skin and mucous membrane agents (AHFS 840408) and are not included in this review. Terbinafine (tablet formulation) is available in a generic formulation. This class was last reviewed in November 2009.

Table 1. Allylamines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Terbinafine	granules, tablet	Lamisil®*	terbinafine

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

The allylamines 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 FDA-approved indications for the allylamines 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 anti-infective 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 Allylamines[1-5]

Organism	Terbinafine
Trichophyton mentagrophytes	✔
Trichophyton rubrum	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Allylamines

Clinical Guideline	Recommendation(s)
European Academy of Dermatology and Venereology (EADV): **Onychomycosis Treatment Guidelines[10] (2005)**	• Prior to initiating treatment, it is important that diagnosis be confirmed and the etiological agent identified. • Topical monotherapy is indicated when the matrix area is not involved. Topical treatment is also suitable for patients who are reluctant to take oral medications or have swallowing difficulties. The only case in which it is not recommended is if nail penetration may be suboptimal. • Oral antifungal drugs are generally considered to be more effective than topical treatments. However, they are accompanied by a higher risk of systemic adverse effects and drug interactions. • Oral monotherapy (terbinafine, itraconazole or fluconazole) or combined oral and topical (nail lacquer) is recommended when 1) at least 50% of the distal nail plate is involved; 2) the nail matrix area is involved; 3) mycological criteria such as the causative agent or agents are known and oral agents can target specific fungi; 4) topical drugs are not indicated when topical drug transport is suboptimal; and 5) oral or combined therapy is also recommended in cases of nail matrix area involvement. • Combination therapy with systemic and topical treatments may be considered when a large portion of the nail plate is affected (>50%), when the nail matrix is involved, and in cases of treatment failure. • Griseofulvin is associated with the poorest mycological cure rate (<30%) and is rarely used. Terbinafine is associated with the highest mycological cure rate (77–100%).
British Association of Dermatologists (BAD): **Guidelines for the Treatment of Onychomycosis[11] (2003)**	• Both topical and oral agents are available for the treatment of fungal nail infection. The primary aim of treatment is to eradicate the organism as demonstrated by microscopy and culture. • Systemic therapy is almost always more successful than topical treatment, which should only be used in superficial white onychomycosis (SWO), possibly very early distal and lateral subungual onychomycosis (DLSO) or when systemic therapy is contraindicated. • Both terbinafine and itraconazole have been shown to be more effective than griseofulvin in dermatophyte onychomycosis and the optimal choice of treatment lies between terbinafine and itraconazole. • Terbinafine is more effective than itraconazole for dermatophyte infection of the nails and should be first-line treatment. Itraconazole may be considered a second-line treatment. • Expected cure rates vary and range from 80%-90% for fingernail infections and 70%-80% for toenail infections.
European Society for Pediatric Dermatology (ESPD): **Guidelines for the Management of Tinea Capitis in Children[40] (2010)**	• Tinea capitis always requires systemic treatment because topical antifungal agents do not penetrate the hair follicle. • Topical treatment is only used as adjuvant therapy to systemic antifungals. • Griseofulvin has been the gold standard for systemic therapy of tinea capitis. The main disadvantage of griseofulvin is the long duration of treatment required (6–12 weeks or longer) which may lead to reduced compliance. • The newer oral antifungal agents including terbinafine, itraconazole, and fluconazole appear to have efficacy rates and potential adverse effects similar to those of griseofulvin in children with tinea capitis due

Clinical Guideline	Recommendation(s)
	to *Trichophyton* species, while requiring much shorter duration of treatment. The decision between griseofulvin and newer antifungal agents for children with *Trichophyton* species can be based on the balance between duration of treatment and compliance. • Griseofulvin is still the treatment of choice for cases caused by *Microsporum* species. • Adjunctive topical therapies, such as selenium sulfide or ketoconazole shampoos, as well as fungicidal creams or lotions have been shown to decrease the carriage of viable spores responsible for the disease contagion and reinfection and may shorten the cure rate with oral antifungals. • The topical fungicidal cream/lotion should be applied to the lesions once daily for a week. The shampoo should be applied to the scalp and hair for 5 minutes twice weekly for 2–4 weeks or three times weekly until the patient is clinically and mycologically cured. The latter in conjunction with 1 week of topical fungicidal cream or lotion application is recommended.

British Association of Dermatologists (BAD): **Guidelines for the Management of Tinea Capitis[12] (2000)**	• The aim of treatment is to achieve a clinical and mycological cure as quickly as possible.
	• Oral antifungal therapy is generally needed. Topical treatment alone is not recommended for the management of tinea capitis.
	• Oral therapy options include griseofulvin, terbinafine, itraconazole, fluconazole, and ketoconazole.
	• If there has been no clinical response and signs persist at the end of the treatment period, then the options include:
	  o Increase the dose or duration of the original drug (both griseofulvin and terbinafine have been used successfully and safely at higher doses or for longer courses to clear resistant infections)
	  o Change to an alternative antifungal (e.g. switch from griseofulvin to terbinafine or itraconazole).
	• Symptom-free carriers with light growth/low spore count on culture may be treated with twice weekly selenium or povidone shampoo.
	• The definitive end-point for adequate treatment is not clinical response but mycological cure; therefore, follow-up with repeat mycology sampling is recommended at the end of the standard treatment period and then monthly until mycological clearance is documented. Treatment should, therefore, be tailored for each individual patient according to response.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the allylamines 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 Allylamines[1-5]

Indication	Terbinafine Tablets	Terbinafine Granules
Treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)	✔	
Treatment of tinea capitis		✔

IV. Pharmacokinetics

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

Table 5. Pharmacokinetic Parameters of the Allylamines[1-5]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Terbinafine	40	99	Hepatic	Renal (70-80) Bile (20)	22-26

V. Drug Interactions

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

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

Generic Name(s)	Significance Level	Interaction	Mechanism
Terbinafine	2	Beta-blockers	Inhibition of cytochrome P450 2D6 isoenzymes by terbinafine may decrease the metabolic elimination of beta-adrenergic blockers. Plasma concentrations and pharmacologic effects of beta-adrenergic blockers may be increased by terbinafine.
Terbinafine	2	Serotonin reuptake blockers	Plasma concentrations and pharmacologic effects of serotonin reuptake blockers may be increased when co-administered with terbinafine. The potential for adverse effects due to serotonin reuptake blockers may be increased. Inhibition of CYP2D6-mediated metabolism of serotonin reuptake blockers by terbinafine is suspected.
Terbinafine	2	Tricyclic antidepressants	Terbinafine may increase pharmacologic effects and plasma concentrations of tricyclic antidepressants. Toxic signs may occur. Inhibition of cytochrome P450 2D6 isoenzymes by terbinafine may decrease the metabolic elimination of tricyclic antidepressants.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the allylamines are listed in Table 7.

Table 7. Adverse Drug Events (%) Reported with the Allylamines[1-5]

Adverse Events	Terbinafine Granules	Terbinafine Tablets
Central Nervous System		
Fatigue	✔	✔
Fever	7	✔
Headache	7	-
Malaise	✔	✔
Dermatological		
Alopecia	✔	✔
Exanthematous pustulosis	✔	✔
Photosensitivity reaction	✔	✔
Pruritus	1	3
Psoriasiform eruption	✔	✔
Psoriasis exacerbation	✔	✔
Rash	2	6
Stevens-Johnson syndrome	✔	✔
Toxic epidermal necrolysis	✔	✔
Urticaria	1	1
Gastrointestinal		
Abdominal pain	2-4	2
Diarrhea	3	6
Dyspepsia	-	4
Flatulence	-	2
Nausea	2	3
Taste disturbance	✔	3
Taste loss	✔	✔
Toothache	1	-
Vomiting	5	✔
Hematological		
Agranulocytosis	✔	✔
Anemia	✔	✔
Neutropenia	✔	✔
Pancytopenia	✔	✔
Thrombocytopenia	✔	✔
Hepatic		
Hepatic failure	✔	✔
Hepatic injury	✔	✔
Liver enzyme abnormalities	-	3
Musculoskeletal		
Arthralgia	✔	✔
Myalgia	✔	✔
Rhabdomyolysis	✔	✔
Respiratory		
Cough	6	-
Nasal congestion	2	-
Nasopharyngitis	10	-
Pharyngolaryngeal pain	2	-
Rhinorrhea	2	-
Upper respiratory tract infection	5	-
Other		
Allergic reactions	✔	✔

Adverse Events	Terbinafine Granules	Terbinafine Tablets
Angioedema	✔	✔
Creatine phosphokinase increased	✔	✔
Influenza-like illness	2	✔
Lupus erythematosus exacerbation	✔	✔
Ocular lens and retina changes	✔	-
Pancreatitis	✔	✔
Serum sickness-like reaction	✔	✔
Smell disturbance	✔	✔
Smell loss	✔	✔
Vasculitis	✔	✔
Visual disturbance	✔	1

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

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

Table 8. Usual Dosing Regimens for the Allylamines[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Terbinafine	Fingernail Onychomycosis: Tablet: 250 mg once daily for 6 weeks Toenail Onychomycosis: Tablet: 250 mg once daily for 12 weeks	Tinea Capitis: ≥4 years of age: <25 kg: 125 mg once daily for 6 weeks 25-35 kg: 187.5 mg once daily for 6 weeks >35 kg: 250 mg once daily for 6 weeks	Granules: 125 mg 187.5 mg Tablet: 250 mg

VIII. Effectiveness

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

Table 9. Comparative Clinical Trials with the Allylamines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Onychomycosis				
Haneke et al.[13] (1995) Terbinafine 250 mg daily for 12 weeks vs griseofulvin microsize 500 mg daily for 12 weeks After 12 weeks of treatment, all patients received an additional 12 weeks of placebo followed by 6 months follow-up.	DB, MC, RCT Patients 18 years of age and older with clinically confirmed distal subungual onychomycosis of the fingernails	N=180 1 year	Primary: Clinical response (outgrowth from the border of healthy and infected nails), mean global score (based on onycholysis, hyperkeratosis, brittleness, and paronychial inflammation), mycological cure (negative culture), mean time to negative culture	Primary: Mycological cure rates increased in both groups during active treatment and continued in the terbinafine group during follow-up while remaining steady in the griseofulvin group. At week 24, 90% of patients in the terbinafine group and 64% in the griseofulvin group were mycologically cured. At the end of the study, 92% of patients in the terbinafine group and 63% in the griseofulvin group were mycologically cured (P<0.001). Mean time to negative culture was 73 days in the terbinafine group and 93 days in the griseofulvin group. The length of unaffected nail increased in the terbinafine group from 3.2 mm to 11.4 mm (week 24) and 12.4 mm (end of study). In the griseofulvin group, it increased from 2.6 mm to 9.5 mm (week 24) and decreased to 8.7 mm at the end of the study (P=0.006 between groups at the end of the study). The mean global scores decreased in the terbinafine group from 5.8 to 0.9 (week 24) and 0.4 (end of study). In the griseofulvin group, the scores decreased from 5.7 to 1.8 (week 24) and increased to 2.2 at the end of the study (P=0.028 at week 24, P<0.001 at end of study).
Faergemann et al.[14] (1995) Terbinafine 250 mg daily for 16 weeks	DB, PG, RCT Adult patients with culture-proven tinea of the toenails	N=89 52 weeks	Primary: Complete cure (no signs and symptoms of infection and negative culture), mycological cure	Primary: Significantly more patients in the terbinafine group were completely cured (42%) compared to the griseofulvin group (2%) at the end of the study (P<0.0005). Significantly more patients in the terbinafine group experienced mycological cure (84%) compared to the griseofulvin group (45%) at the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs griseofulvin 500 mg daily for 52 weeks Patients who did not respond after 16 weeks were switched to OL terbinafine for 16 to 20 weeks of follow-up.			(negative culture)	end of the study (P<0.0005). Of the patients who switched to open-label treatment with terbinafine, 44% were cured at the end of the study (week 52 or 20 weeks after cessation of open-label terbinafine) compared to 18% in the griseofulvin group.
Hoffman et al.[15] (1995) Terbinafine 250 mg daily for 24 weeks, followed by placebo for 24 weeks vs griseofulvin micronized 1,000 mg daily for 48 weeks	DB, RCT Patients 21-93 years of age with clinically confirmed distal subungual onychomycosis of the toenails	N=195 72 weeks	Primary: Mycological cure (negative culture), clinical response (global score based on growth of unaffected nail and presence of onycholysis, hyperkeratosis, brittleness, and paronychial inflammation), time to mycological cure	Primary: Mycological cure increased during active therapy in both groups and slightly decreased in the terbinafine group while sharply decreasing in the griseofulvin group during the follow-up period. At week 48, 88% of terbinafine patients and 82% of griseofulvin patients had negative cultures, while these numbers decreased to 81% and 62%, respectively, at the end of the study (P=0.02). The time to negative culture was 130 days in the terbinafine group and 172 days in the griseofulvin group (P=0.036). The mean global score in the terbinafine group decreased from 6.3 to 1.4 at week 48 and 0.8 at the end of the study, compared to 7.0 in the griseofulvin group decreasing to 1.7 at week 48 and 1.8 at the end of the study (P=0.010).
Haugh et al.[16] (2002) Terbinafine 250 mg daily for 3 to 6 months	MA Patients diagnosed with onychomycosis	N=2,063 3 to 11 months	Primary: Mycological cure at the end of the studies (negative microscopy or culture), negative microscopy or	Primary: <u>Terbinafine vs placebo (3 trials)</u> After 12 weeks, a significant advantage in mycological cure rates was seen in favor of the terbinafine group compared to the placebo group. <u>Terbinafine vs itraconazole (4 trials)</u> At the end of the study periods, a statistically significant advantage in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs griseofulvin 500 to 1,000 mg daily for 3 months to 11 months vs itraconazole 200 mg daily or 400 mg intermittently (for 1 of every 4 weeks) for 3 to 4 months vs placebo			culture at specified time points	achieving negative culture and microscopy was seen in favor of terbinafine compared to itraconazole. No significant differences in the occurrence of adverse events were reported. <u>Terbinafine vs griseofulvin (2 trials)</u> Significantly higher rates of negative microscopy and culture were observed in the terbinafine groups at week 24 compared to the griseofulvin groups.
Brautigam[17] (1998) Terbinafine 250 mg daily for 12 weeks vs itraconazole 200 mg daily for 12 weeks	DB, MC, PG, RCT Patients 18 years of age and older with a clinical diagnosis of distal subungual or proximal onychomycosis of the toenails	N=195 52 weeks	Primary: Mycologic cure (culture negative for dermatophytes and hyphae), clinical efficacy (length of unaffected area on the target nail)	Primary: Significantly more patients in the terbinafine group had experienced mycological cure (81.4%) compared to the itraconazole group (63.1%, P<0.01) at week 52. At week 52, 91.9% of cultures were negative for dermatophytes in the terbinafine group compared to 66.6% in the itraconazole group (P<0.0001). The mean time to the first negative culture was significantly shorter in the terbinafine group (8.52 weeks) compared to the itraconazole group (11.64 weeks, P<0.05). Terbinafine was significantly more effective in increasing the length of unaffected nail compared to itraconazole. At week 52, a significantly lower number of patients in the terbinafine group had >60% of the nail plate affected (3.5% of patients) compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the number in the itraconazole group (15.5% of patients, P<0.05).
Evans et al.[18] (1999) Terbinafine 250 mg daily for 12 to 16 weeks vs itraconazole 200 mg daily for 1 of every 4 weeks for 12 (3 cycle) or 16 weeks (4 cycle)	DB, MC, PG, RCT Patients 18-75 years of age with a clinical diagnosis of onychomycosis of the toenail confirmed by positive results on mycological cure and microscopy	N=496 72 weeks	Primary: Mycologic cure (negative results on microscopy and culture) Secondary: Clinical cure (100% toenail clearing), complete cure (mycological and clinical cure), clinical effective-ness (mycological cure and at least 5 mm of new clear toenail growth), and global assessments by physician and patient	Primary: Mycologic cure rates were significantly higher in both terbinafine groups (81% and 80% respectively) compared to the itraconazole groups (41% and 53% for the 3-cycle and 4-cycle itraconazole groups respectively, P<0.0001). Secondary: Clinical cure rates were significantly higher in the terbinafine groups compared to the itraconazole groups (P<0.0022). Complete cure rates were significantly higher in the continuous terbinafine group compared to both itraconazole groups (P<0.0044). Clinical effectiveness and global assessments were significantly higher for the continuous terbinafine groups compared to the itraconazole groups (P<0.0001).
Degreef et al[19] (1999) Terbinafine 250 mg daily for 12 weeks vs itraconazole 200 mg daily for 12 weeks	DB, MC, PG, RCT Patients 18-65 years of age with clinically suspected and microscopically and culturally proven onychomycosis of the toenail	N=297 36 weeks	Primary: Mycologic cure (culture negative) Secondary: Investigator's global clinical evaluation of response to treatment defined as clinical response (cured or markedly improved, ≥50% clinical improve-ment), percentage	Primary: A similar number of patients were mycologically cured (79 in the terbinafine group and 78 in the itraconazole group). Secondary: Clinical response rates were similar between the groups (P<0.1). Complete clinical cure rates were similar between the groups. The mean percentage of affected nail area and the mean number of nails infected decreased similarly in the two groups. Signs and symptoms of infections improved comparably in the two groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			of total affected nail area, total number of infected nails, signs and symptoms of onycholysis, hyperkeratosis, paronychial inflammation and discoloration	
Gupta et al.[20] (2001) Terbinafine 250 mg daily for 12 weeks vs itraconazole 200 mg 2 times daily for 1 week given as 3 pulses	CS, PRO, RCT, SB Patients 60 years of age and older with dermatophyte onychomycosis of at least 1 great toe	N=101 18 months	Primary: Mycologic cure (negative cultures), clinical efficacy (mycological cure and either clinical cure or reduction of involved nail plate to 10% or less)	Primary: At month 18, the mycological cure rate in the terbinafine group was 64% and 62.7% in the itraconazole group. No significant difference was found between groups. At month 18, clinical efficacy was 62% in the terbinafine group and 60.8% in the itraconazole group. No significant difference was found between groups.
Sigurgeirsson et al.[21] (2002) Terbinafine 250 mg daily for 12 or 16 weeks vs itraconazole 400 mg daily for 1 of every 4 weeks for 12 (3 cycles) or 16	DB, PRO, RCT Patients 18-75 years of age with onychomycosis of the toenail confirmed by culture finding infection with a dermatophyte	N=158 72 weeks	Primary: Proportion of patients who remained mycologically cured (negative culture) at the end of follow-up without requiring continued treatment with terbinafine Secondary: Clinical cure	Primary: Significantly more patients originally treated with terbinafine were mycologically cured at the end of the study compared to patients originally treated with itraconazole (46% compared to 13%, P<0.001). Secondary: Significantly more patients originally treated with terbinafine were clinically cured at the end of the study compared to patients originally treated with itraconazole (42% compared to 18%, P<0.002). Significantly more patients in the terbinafine group maintained complete cure at the end of the study compared to patients in the itraconazole group (P<0.005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(4 cycles) weeks			(100% normal-appearing nail), complete cure (mycological plus clinical cure), clinical and mycological relapse over time, mycological and clinical cure over time, effect of subsequent terbinafine treatment on clinical and mycological outcome	At the end of the study, significantly fewer terbinafine patients had mycologically relapsed compared to itraconazole patients (23% compared to 53%, P<0.01). At the end of the study, significantly fewer terbinafine patients had clinically relapsed compared to itraconazole patients (21% compared to 48%, P<0.05). Ninety-two percent of patients who originally received terbinafine and subsequently received a second course of treatment with terbinafine after 18 months achieved mycological cure compared to 85% of those originally treated with itraconazole. Similar results were seen with clinical cure rates: it was achieved in 76% of patients originally treated with terbinafine and 77% of patients originally treated with itraconazole.
Sigurgeirsson et al.[22] (1999) Terbinafine 250 mg daily for 12 weeks (group T_{12}) or 16 weeks (group T_{16}) vs itraconazole 400 mg/day for 1 week every 4 weeks for 12 weeks (group I_3) or 16 weeks (group I_4)	DB, DD, MC, PG, PRO, RCT Patients 18-75 years of age with distal subungual or total dystrophic onycho-mycosis of the toenails confirmed mycologically	N=507 72 weeks	Primary: Mycological cure (negative microscopy and cultures) Secondary: Clinical cure (100% toenail clearing), complete cure (mycological and clinical cure), clinical efficacy (mycological cure and at least 5 mm of new clear toenail growth), global assessment of efficacy by patient and	Primary: Mycological cure rates were 75.7% in the T_{12} group, 80.8% in the T_{16} group, 38.3% in the I_3 group and 49.1% in the I_4 group. Results were statistically significant in favor of the terbinafine regimens (P<0.0001). Secondary: Clinical cure was 53.6%, 60.2%, 31.8%, and 32.1% for the T_{12}, T_{16}, I_3, and I_4 groups respectively, and all were significantly in favor of the terbinafine regimens (P<0.002). Complete cure rates were 45.8%, 55.1%, 23.4%, and 25.9% for the T_{12}, T_{16}, I_3, and I_4 groups respectively, and all were significantly in favor of the terbinafine regimens (P<0.0007). Clinical efficacy rates were significantly in favor of the terbinafine regimens (P<0.0001). Global assessment of efficacy by patients was very good or excellent in 78.9%, 78.8%, 43.9%, and 52.3% of patients in the T_{12}, T_{16}, I_3, and I_4 groups, respectively, and were statistically in favor of the terbinafine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			physician	regimens (P<0.0001). Global assessment of efficacy by physicians was very good or excellent in 78.9%, 78.8%, 43.9%, and 52.3% of patients in the T_{12}, T_{16}, I_3, and I_4 groups, respectively, and these assessments statistically favored the terbinafine regimens (P<0.0001).
Heikkila et al.[23] (2002) Terbinafine 250 mg daily for 12 or 16 weeks vs itraconazole 400 mg daily for 1 of every 4 weeks for 12 (3 cycles) or 16 (4 cycles) weeks	DB, MC, RCT Finnish participants 18-75 years of age with a clinical diagnosis of onychomycosis of the toenail confirmed by culture	N=76 4 years	Primary: Mycologic cure (microscopy and culture negative), clinical cure (100% clearing of all toenails), complete cure (mycological and complete cure)	Primary: At 4 years, terbinafine was shown to be more effective than itraconazole. At 4 years, negative microscopy and culture remained unchanged in the terbinafine group treated for 16 weeks, but fell to <50% in all other groups. At 4 years, clinical and complete cure rates in the terbinafine group treated for 16 weeks was better than the rates seen at 72 weeks (78% compared to 50%), but remained unchanged or worsened in all other groups.
De Backer et al.[24] (1998) Terbinafine 250 mg daily for 12 weeks vs itraconazole 200 mg daily for 12 weeks	DB, RCT Patients 18 years of age and older with clinically suspected subungual dermato-phyte infections of the toenails confirmed by microscopy and culture	N=372 48 weeks	Primary: Percentage of patients with negative culture at week 48, length of healthy nail, hyperkeratosis, onycholysis, paronychial inflammation, investigator and patient assessment of efficacy of treatment	Primary: At week 48, significantly more patients in the terbinafine group had negative microscopy results (77.9%) compared to the itraconazole group (55.4%, P<0.0001). At week 48, significantly more patients in the terbinafine group had negative dermatophyte culture results (84%) compared to the itraconazole group (64.3%, P<0.0001). At week 48, significantly more patients in the terbinafine group had negative mycology results (73%) compared to the itraconazole group (45.8%, P<0.0001). At week 48, patients in the terbinafine group had significantly more healthy nail in the big toe compared to the itraconazole group (8.1 mm and 6.4 mm respectively, P=0.026). At week 48, onycholysis score significantly favored terbinafine compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				to itraconazole (P=0.001). There was no significant difference in hyperkeratosis scores between groups (P=0.27). Paronychial inflammation was absent in the majority of patients in both groups. The global clinical evaluation of the target nail at week 48 was significantly higher in the terbinafine group (cleared or minimal symptoms) compared to the itraconazole group (76.2% and 58.1% respectively, P=0.001).
De Backer et al.[25] (1996) Terbinafine 250 mg daily for 12 weeks vs itraconazole 200 mg daily for 12 weeks	DB, RCT Patients with a clinical diagnosis of toenail onychomycosis	N=372 48 weeks	Primary: Clinical symptoms, rate of negative mycology (negative microscopy and negative culture)	Primary: Clinical symptoms in the target nail improved significantly more in the terbinafine group compared to the itraconazole group (P=0.001). The unaffected nail length for big toes was significantly greater in the terbinafine group compared to the itraconazole group (9.1 mm and 7.7 mm respectively, P=0.0298). Onycholysis was less frequent in the terbinafine group compared to the itraconazole group (P=0.001). No significant difference was seen between groups in hyperkeratosis. Negative mycology was observed in 73% of terbinafine patients compared to 45.8% of itraconazole patients at week 48 (P<0.0001).
Arenas et al.[26] (1995) Terbinafine 250 mg daily for 3 months vs itraconazole 200	CS, OL, PRO Patients 18 years of age and older with onychomycosis	N=53 9 months	Primary: Culture and potassium hydroxide (KOH) smear results, affected nail area, medical evaluation of treatment (cure, improvement, no changes,	Primary: At the end of treatment, rates of positive KOH smears were similar between groups (21.7% for itraconazole and 23.5% for terbinafine). At the end of treatment, there was 1 positive culture in the terbinafine group and at the end of follow-up, there was 1 positive culture in the itraconazole group. Both treatment groups showed improvement in nail area affected compared to baseline (P<0.01) and there was no significant difference

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg daily for 3 months			deterioration) Secondary: Nail changes, nail growth, patient evaluation of treatment	between groups. There was no significant difference between groups in the medical evaluation of treatment. There was no significant difference in cure and improvement between groups. Secondary: There were no significant differences in nail changes or nail growth between groups. There was no significant difference between groups in the patients' evaluation of treatment.
Bahadir et al.[27] (2000) Terbinafine 250 mg daily for 3 months vs itraconazole 100 mg 2 times daily for the first week of 3 consecutive months	RCT Patients with clinically and mycologically confirmed onychomycosis	N=60 24 week posttreatment follow-up	Primary: Therapeutic response (healing, remission, or failure, undefined)	Primary: Healing was achieved in 60% of itraconazole patients and 68.5% of terbinafine patients (P=0.50). Remission was achieved in 28% of itraconazole patients and 25.7% of terbinafine patients (P=0.50). Failure was reported in 4% of itraconazole patients and 2.85% of terbinafine patients (P=0.50).
Honeyman et al.[28] (1997) Terbinafine 250 mg daily for 4 months vs	DB, MC, PG, RCT Patients with toenail onychomycosis	N=179 12 months	Primary: Clinical response (symptom scores), mycological response (negative culture), clinical global evaluation scores [CGE, defined as	Primary: At the end of treatment (4 months), mycological cure was similar for terbinafine and itraconazole (54.9% and 51.8%, respectively). At 12 months, the mycological cure was 95.3% for terbinafine and 84.3% for itraconazole (P=0.04). No significant differences in clinical response were observed between groups at month 4 or 12 (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
itraconazole 200 mg daily for 4 months Patients in both groups received placebo for an additional 8 months after initial therapy.			complete cure, improvement (reduction of >50%), unchanged, or worsening], effectively cured patient scores (ECP, defined as complete mycological cure plus clinical improvement or complete cure)	There was no significant difference in the CGE at month 4 or 12 between groups when clinical cure was considered, though when clinical improvement was also considered, terbinafine showed significantly better scores (P<0.02). At 4 months, there was no difference in the proportion of patients considered to be ECP, though at 12 months significantly more patients in the terbinafine group were considered ECP (95.3% and 75.7%, respectively; P<0.001).
Brautigam et al.[29] (1995) Terbinafine 250 mg daily for 12 weeks vs itraconazole 200 mg daily for 12 week	MC, RCT Patients with a clinical diagnosis of distal subungual or proximal onychomycosis and a growth of dermatophytes	N=170 40 week posttreatment follow-up	Primary: Mycological response (negative culture), area of unaffected nail	Primary: Mycological cure rates were 81% in the terbinafine group and 63% in the itraconazole group (P<0.01). The length of unaffected nail increased to 9.4 mm in the terbinafine group and to 7.9 mm in the itraconazole group (P<0.05).
Tosti et al.[30] (1996) Terbinafine 250 mg daily (T250) vs terbinafine 500 mg daily for 1 week every month (T500)	OL, RCT Patients with onychomycosis of the toenails or fingernails	N=63 6 month posttreatment follow-up	Primary: Mycological response (not cured, cured with residual malformations, cured without residual malformations)	Primary: At the end of the follow-up period, 76.5% of patients in the T250 group were cured without residual malformations compared to 50% in the T500 group and 38.1% in the I group (P=0.013 between T250 and I). At the end of the follow-up period, significantly more patients in the I group were considered cured with residual malformations compared to those in the T250 group (P=0.013). At the end of the follow-up period, significantly more patients in the I group were considered failures compared to those in the T250 group (P=0.013).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs itraconazole 400 mg daily for 1 week every month (I) Treatment was continued for 4 months for toenail infections and for 2 months for fingernail infections.				
Chang et al.[33] (2007) Terbinafine, itraconazole, fluconazole (with or without topical agents)	MA Patients aged ≥18 years with superficial dermatophytosis (tinea pedis, tinea manus, tinea corpora, and tinea cruris) or onychomycosis who were receiving oral antifungal therapy for 2 or more weeks	N=19,298 (122 trials) Variable duration	Primary: Cumulative incidence of patients who withdrew from the study because of adverse reactions Secondary: Cumulative incidence of patients stopping treatment because of elevation of serum transaminase levels and cumulative incidence of patients developing elevation of serum transaminase levels	Primary: For continuous oral antifungal therapy, the pooled risks of treatment discontinuation because of adverse reactions were 3.44% (95% CI, 2.28%-4.61%) for terbinafine 250 mg/day; 1.96% (95% CI, 0.35%-3.57%) for itraconazole 100 mg/day; 4.21% (95% CI, 2.33%-6.09%) for itraconazole 200 mg/day; and 1.51% (95% CI, 0%-4.01%) for fluconazole 50 mg/day. For intermittent or pulse therapy, the pooled risks of treatment discontinuation because of adverse reactions were 2.09% (95% CI, 0%-4.42%) for terbinafine; 2.58% (95% CI, 1.15%-4.01%) for itraconazole; 1.98% (95% CI, 0.05%-3.92%) for fluconazole 150 mg/week and 5.76% (95% CI, 2.42%-9.10%) for fluconazole 300 to 450 mg/week. Secondary: The incidence of liver injury associated with oral antifungal therapy was less than 2% in general. For the risks of having elevated serum transaminase levels that required treatment termination, the pooled risk estimates for continuous therapy ranged from 0.11% (itraconazole 100 mg/day) to 1.22% (fluconazole 50 mg/day). The pooled risk estimates for pulse therapy ranged from 0.39% (fluconazole 150 mg/week and itraconazole 400 mg/day) to 0.85%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			during treatment but not requiring discontinuation	(fluconazole 300-450 mg/week). The pooled risks of developing elevated serum transaminase levels not requiring treatment discontinuation was on the order of 1.5% for continuous regimens and 1% for intermittent regimens evaluated.
Tinea Capitis				
Elewski et al.[31] (2008) Terbinafine granules 125 to 250 mg (5-8 mg/kg) once daily for 6 weeks vs griseofulvin suspension 125 to 500 mg (10-20 mg/kg) once daily for 6 weeks	RCT, SB, MC (Pooled analysis of 2 trials) Children between 4 and 12 years of age with a clinical diagnosis of tinea capitis confirmed by positive potassium hydroxide microscopy at baseline	N=1,549 10 weeks	Primary: End-of-study complete cure rate defined as mycologic cure (negative culture and microscopy) and clinical cure Secondary: End-of-study mycologic cure rate, end-of-study clinical cure rate, and adverse events	Primary: The complete cure rate at the end-of-study (week 10) was statistically higher in the terbinafine group (45.1%) compared to the griseofulvin group (39.2%; P=0.024) in the pooled analysis. In the individual analyses, terbinafine was more effective than griseofulvin in trial 1 (46.23% vs 34.01%, respectively; P<0.01) but not in trial 2 (43.99% vs 43.46%, respectively; P=0.95). Secondary: The end-of-study mycologic cure rate was higher in the terbinafine group (61.5%) compared to the griseofulvin group (55.5%; P=0.029). In the individual analyses, terbinafine was more effective than griseofulvin in trial 1 (62.29% vs 50.25%; P<0.01) but not in trial 2 (60.77% vs 59.92%; P=0.89). The end-of-study clinical cure rate were similar between terbinafine and griseofulvin in the pooled analysis (63% vs 58.8%; P=0.10) as well as in the individual trials (trial 1: 62.77% vs 56.35%; P=0.06; trial 2: 63.27% vs 60.76%; P=0.59). Overall, 51.9% of patients in the terbinafine group and 49.1% of patients in the griseofulvin group reported an adverse event during the study. The incidence of adverse events by organ class was similar in the two treatment groups.
Lipozencic et al.[34] (2002) Terbinafine tablets 125 to 250 mg daily for 6 to 12 weeks	DB, MC, PG, RCT Patients 4 years of age and older diagnosed with tinea capitis clinically confirmed	N=134 16 weeks	Primary: Complete cure at the end of study (EOS) defined by negative culture and no residual signs and	Primary: There was no significant difference between any of the terbinafine treatment groups in complete cure at EOS (P=0.12). Higher daily doses of terbinafine (>4.5 mg/kg/day) had a positive effect on complete cure rates at EOS compared to lower doses (<4.5 mg/kg/day) (P=0.048).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs griseofulvin oral suspension 20 mg/kg/day for 12 weeks	by positive culture for *Microsporum* species		symptoms Secondary: Effective treatment (negative culture and minimal signs and symptoms), clinical cure (no clinical signs and symptoms), mycological cure (negative microscopy and culture)	Open-label, high-dose griseofulvin showed a high rate of complete cure at EOS of 84%. No comparisons were made between griseofulvin group and terbinafine groups. Secondary: At EOS, no significant differences were observed between any of the terbinafine treatment groups in any secondary endpoint (P>0.05). Open-label, high-dose griseofulvin produced effective treatment in 88% of patients, mycological cure in 76%, and clinical cure in 96%. No comparisons were made between the griseofulvin and terbinafine groups.
Fuller et al.[35] (2001) Terbinafine tablets 62.5 mg to 125 mg daily for 4 weeks vs griseofulvin suspension 10 mg/kg/day for 4 weeks Patients used selenium sulfide shampoo at least 2 times weekly for the first 2 weeks.	MC, OL, PG, RCT Patients 2-16 years of age with a diagnosis of tinea capitis confirmed by culture	N=210 24 weeks	Primary: Clinical response (complete cure= microscopy and culture negative, no residual signs and symptoms; cure= microscopy and culture negative and total symptom score $\leq$2)	Primary: No significant differences were observed between groups in clinical response (P>0.2). Graphical representation of cure rates shows a numerically higher response to terbinafine at earlier time points. Significantly more children weighing over 20 kg and infected with *Trichophyton* species were rated as cured at week 4 compared to children in the griseofulvin group (36% and 13%, respectively; P=0.03).
Caceres-Rios et al.[36]	DB, PRO, RCT	N=50	Primary: Clinical outcomes	Primary: At the end of week 8, the efficacy (as measured by complete cure) of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2000) Terbinafine tablets 62.5 to 250 mg daily for 4 weeks, then 4 weeks of placebo vs griseofulvin 125 to 500 mg daily for 8 weeks	Patients 1-14 years of age with a clinical and mycological diagnosis of non-inflammatory tinea capitis	12 weeks	(complete cure= negative culture and resolution of signs and symptoms; mycological cure= negative mycological findings and slight erythema, desquamation or pruritus)	griseofulvin was 76% and 72% for terbinafine. No significant difference between groups was observed. At the end of week 8, no significant difference was observed between the groups with respect to proportion of patients with negative cultures. At the end of week 12, the proportion of patients with negative cultures decreased in the griseofulvin group and increased or remained steady in the terbinafine group. A significant difference in favor of the terbinafine group was observed (P<0.05). At the end of week 12, the efficacy (as measured by complete cure) of griseofulvin had decreased to 44% and terbinafine had risen to 76% (P<0.05).
Memisoglu et al.[39] (1999) Terbinafine once daily for 4 weeks vs griseofulvin once daily for 8 weeks	RCT, DB Children with mycologically proven tinea capitis	N=78 12 weeks	Primary: Mycological cure, effective treatment (complete disappearance of signs/symptoms and negative mycology, or not >2 signs/symptoms of mild erythema, desquamation or pruritus)	Primary: At week 12, a mycological cure was recorded in 88.0% of the terbinafine-treated group, compared with 91.0% of the griseofulvin-treated group. Effective treatment was recorded in 78% of patients in the terbinafine-treated group compared with 74% of patients in the griseofulvin-treated group. *Trichophyton* species and *Microsporum canis* showed similar responsiveness to terbinafine treatment.
Fleece et al.[37] (2004) Terbinafine administered for 2 to 4 weeks vs griseofulvin administered for 6	MA Patients with tinea capitis	N=603 (6 trials) 12 to 16 weeks	Primary: Clinical outcomes	Primary: Three separate meta-analyses were performed. Analysis I included all 6 studies using culture status at least 12 weeks after enrollment in the study as the outcome. The OR was 0.86 (95% CI: 0.57–1.27; P=0.444). Analysis II included only the 5 studies in which *Trichophyton* species were the predominant pathogens and outcome was assessed at least 12 weeks post-enrollment. The OR was 0.65 (95% CI: 0.042–1.01; P=0.054).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 8 weeks				Analysis III included the 4 studies that provided outcome data at 8 weeks post-enrollment. The OR was 0.84 (95% CI: 0.54 –1.32; P=0.462).
González et al.[32] (2007) Terbinafine, itraconazole, fluconazole, ketoconazole, griseofulvin	MA Children <18 years of age with tinea capitis confirmed by microscopy or growth of dermatophytes in culture or both	N=1,812 (21 trials) 6 to 26 weeks	Primary: The proportion of participants with complete cure (clinical and mycological)	Primary: <u>Terbinafine vs griseofulvin:</u> A pooled analysis of the five trials found that the difference in the cure rates between four weeks of terbinafine and eight weeks griseofulvin was not statistically significant (RR 1.11; 95% CI, 0.96 to 1.29). <u>Itraconazole vs griseofulvin:</u> In the pooled analysis, there was no significant difference in cure rates between itraconazole and griseofulvin (RR 0.94; 95% CI, 0.80 to 1.09). <u>Itraconazole vs terbinafine:</u> In the pooled analysis, there was no significant difference in cure rates between itraconazole and terbinafine (as treatment of *Trichophyton* species) when used for periods of two to three weeks (RR 0.93; 95% CI, 0.72 to 1.19). <u>Ketoconazole vs griseofulvin:</u> In the pooled analysis, there was no significant difference in cure rates between ketoconazole and griseofulvin (RR 0.72; 95% CI, 0.50 to 1.02). <u>Fluconazole vs griseofulvin:</u> In the pooled analysis, there was no significant difference in cure rates between fluconazole and griseofulvin (RR 0.92; 95% CI, 0.80 to 1.05). <u>Fluconazole vs terbinafine:</u> In one study, the cure rates were found to be similar between fluconazole and terbinafine (RR 0.87; 95% CI, 0.75 to 1.01). <u>Fluconazole vs itraconazole:</u> In one study, the cure rates were found to be similar between fluconazole and itraconazole (RR 1.00; 95% CI, 0.83 to 1.20).
Tey et al.[9] (2011) Terbinafine	MA Children and adults with a diagnosis of	N=2,163 (7 trials) Variable	Primary: Complete cure rate (defined as the achievement of	Primary: The pooled OR did not significantly favor griseofulvin or terbinafine when all studies were pooled (OR, 1.22; 95% CI, 0.785-1.919; P=0.37).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs griseofulvin	tinea capitis	duration	both clinical and mycological cure) Secondary: Mycological cure rate (defined as the absence of dermatophytes on microscopy and culture), clinical cure rate (defined as the resolution of clinical symptoms and signs), adverse events	For those studies with *Trichophyton* species being the predominant pathogen, the pooled OR favored terbinafine, but did not reach statistical significance (OR, 1.49; 95% CI, 0.975-2.277; P=0.065). For those studies with *Microsporum* species being the predominant pathogen, the pooled OR significantly favored griseofulvin (OR, 0.408; 95% CI, 0.254-0.656; P<0.001). Griseofulvin was associated with a small number of adverse effects including gastrointestinal symptoms, headache, upper respiratory tract symptoms, and rash. Severe adverse effects did not occur. The most frequent adverse events reported with terbinafine were gastrointestinal symptoms and upper respiratory tract symptoms. One patient developed asymptomatic neutropenia that was reversible after treatment was terminated prematurely.
Miscellaneous				
Francesconi et al.[38] (2011) Terbinafine 250 to 500 mg/day vs itraconazole 100 to 200 mg/day	Cohort Patients diagnosed with cutaneous sporotrichosis	N=304 12 months	Primary: Clinical cure rate (defined as complete healing of the lesions) Secondary: Frequency of recurrence	Primary: The clinical cure rate was similar with terbinafine (92.7%) and itraconazole (92.0%; RR, 1.01; 95% CI, 0.93–1.09). Secondary: The mean time until achieving clinical cure did not differ between the two groups (terbinafine: 11.5 weeks; itraconazole: 11.8 weeks). In the terbinafine group, the duration of treatment until cure ranged from 2 to 24 months. One patient presented recurrence 3 months after the end of treatment. In the itraconazole group, 92.0% of patients were cured within a period of time of 2–44 months. Three patients presented recurrence. No difference in the frequency of adverse events was observed between the two groups (terbinafine group: 7.3%; itraconazole group: 7.6%; RR, 0.91; 95% CI, 0.39–2.07).

Study abbreviations: CS=comparative study, DB=double blind, DD=double dummy, MA=meta-analysis, MC=multi-center, OL=open label, OR=odds ratio, PG=parallel group, PRO=prospective trial, RCT=randomized controlled trial, SB=single blind

Additional Evidence

Dose Simplification:
Several studies have compared the continuous use of terbinafine with pulse doses of itraconazole.[18,20-23,27,30] Two studies demonstrated similar clinical and mycological outcomes between terbinafine and itraconazole.[20,27] Whereas, five other studies have demonstrated greater efficacy with the continuous use of terbinafine compared to pulse dosing with itraconazole.[18,21-23,30]

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 Allylamines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Terbinafine	granules, tablet	Lamisil®*	$$$$$	$

*Generic is available in at least one dosage form or strength.

X. Conclusions

Terbinafine is approved for the treatment of onychomycosis and tinea capitis.[1-5] The tablet formulation is available generically. For the treatment of onychomycosis, guidelines recommend the use of systemic antifungals as they are generally more effective than topical treatments.[10-11] Oral monotherapy or combined oral/topical therapy is recommended as initial therapy.[10] Terbinafine should be considered as a first-line treatment option and itraconazole may be considered as a second-line treatment.[11] Numerous clinical trials have demonstrated improved clinical and/or mycological cure rates with terbinafine compared to itraconazole and griseofulvin.[13-18,21-25,28-30] Relatively few studies have demonstrated similar cure rates between terbinafine and itraconazole.[19-20,26-28]

For the treatment of tinea capitis, guidelines recommend the use of systemic antifungals because topical agents do not penetrate the hair follicle.[12,40] Fluconazole, itraconazole, griseofulvin and terbinafine have similar efficacy and safety profiles for the treatment tinea capitis due to *Trichophyton* species.[12,40] Griseofulvin is recommended as

initial therapy for the treatment of tinea capitis due to *Microsporum* species.[40] Two studies evaluated the efficacy and safety of terbinafine granules. A pooled analysis demonstrated a higher cure rate with terbinafine granules compared to griseofulvin suspension.[31] However, in the individual analyses of the studies, terbinafine was more effective than griseofulvin in trial 1, but not in trial 2. Similar results were found when the investigators evaluated mycological cure rates. Studies conducted with terbinafine tablets have demonstrated similar cure rates compared to griseofulvin.[9,32,35-37,39] There were no studies found in the medical literature that directly compared terbinafine tablets and granules for the treatment of tinea capitis.

There is insufficient evidence to support that one brand allylamine 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 allylamines 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 allylamine 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Azoles
AHFS Class 081408
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I. Overview

The azoles are approved to treat a variety of fungal infections, including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcal disease, histoplasmosis, sporotrichosis and tinea infections.[1-8] They exert their antifungal activity by interfering with cytochrome P450 activity, decreasing ergosterol synthesis and inhibiting cell membrane formation.

The azoles that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The topical antifungals were previously reviewed with the skin and mucous membrane agents (AHFS 840408) and are not included in this review. All of the products are available in a generic formulation, with the exception of posaconazole. This class was last reviewed in November 2009.

Table 1. Azoles Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Fluconazole	injection, suspension, tablet	Diflucan®*	fluconazole
Itraconazole	capsule, solution	Sporanox®*	itraconazole
Ketoconazole	tablet	N/A	ketoconazole
Posaconazole	suspension	Noxafil®	none
Voriconazole	injection, suspension, tablet	Vfend®*, Vfend IV®	voriconazole

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

The azoles 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 FDA-approved indications for the azoles 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 anti-infective 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 Azoles[1-8]

Organism	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Aspergillus flavus				✔	✔
Aspergillus fumigatus		✔		✔	✔
Aspergillus niger					✔
Aspergillus terreus					✔
Blastomyces dermatitidis		✔	✔		
Candida albicans	✔			✔	✔
Candida glabrata	✔				✔
Candida krusei					✔
Candida parapsilosis	✔				✔
Candida tropicalis	✔				✔
Candida species		✔	✔		
Coccidioides immitis		✔	✔		
Cryptococcus neoformans	✔	✔			
Epidermophyton species			✔		
Fusarium solari					✔
Fusarium species					✔

Organism	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Histoplasma capsulatum			✔		
Histoplasma duboisii		✔			
Microsporum species			✔		
Paracoccidioides brasiliensis		✔	✔		
Phialophora species			✔		
Scedosporium apiospermum					✔
Sporothrix schenckii		✔			
Trichophyton mentagrophytes		✔			
Trichophyton rubrum		✔			
Trichophyton species			✔		

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Azoles

Clinical Guideline	Recommendation(s)
American Thoracic Society (ATS): **Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients[9] (2011)**	<u>Histoplasmosis (Immunocompetent Hosts with *Histoplasma*-related Pulmonary Nodules, Broncholithiasis, or Fibrosing Mediastinitis)</u> • Among asymptomatic patients with pulmonary nodules in whom *Histoplasma* cannot be cultured, antifungal treatment is not recommended. • In most patients with broncholithiasis, antifungal treatment is not recommended. • In patients with fibrosing mediastinitis, some clinicians recommend itraconazole 200 mg twice daily for 12 weeks. In patients with radiographic or physiologic improvement after an initial 12 weeks of therapy, longer treatment, up to 12 months, is recommended. <u>Histoplasmosis (Immunocompetent Hosts with Symptomatic, Progressive, or Severe Pulmonary Histoplasmosis)</u> • In asymptomatic patients, no antifungal treatment is recommended. • In symptomatic patients with mild pulmonary histoplasmosis, who remain symptomatic after 3 weeks of observation, itraconazole 200 mg twice daily for up to 12 weeks is recommended. • In selected patients with mild to moderate pulmonary histoplasmosis, initiating treatment with itraconazole 200 mg twice daily rather than with amphotericin B is recommended. • In patients with severe pulmonary histoplasmosis, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed or until a cumulative dose of 2 g of amphotericin B is reached. In patients who improve clinically after initial treatment with amphotericin B, maintenance itraconazole 200 mg twice daily for at least 12 weeks is recommended. <u>Histoplasmosis (Immunocompromised Hosts with Pulmonary Histoplasmosis or with Progressive or Disseminated Disease, or With Chronic Pulmonary Histoplasmosis)</u> • In patients with mild to moderate histoplasmosis, itraconazole 200 mg three times daily for 3 days is recommended, followed by 200 mg twice daily for 12 months. • In patients with severe progressive disseminated histoplasmosis requiring hospitalization, amphotericin B 0.7–1.0 mg/kg/day (or a lipid formulation of amphotericin 3–5 mg/kg/d) is recommended until clinical improvement is observed or until a cumulative dose of 2 g of amphotericin B is reached. In patients who improve clinically after

Clinical Guideline	Recommendation(s)

	initial treatment with amphotericin B, itraconazole 200 mg twice daily for 12 months is recommended.
	• In patients with AIDS and progressive disseminated histoplasmosis who completed 12 months of initial itraconazole therapy, itraconazole 200 mg twice daily is recommended until effective immune reconstitution occurs.
	• In patients with chronic pulmonary histoplasmosis, itraconazole 200 mg twice daily for 12 to 24 months is recommended rather than no antifungal treatment.
	• In patients with severe chronic pulmonary histoplasmosis, initial treatment with amphotericin B is recommended over itraconazole.
	<u>Sporotrichosis</u>
	• In patients with mild to moderately severe pulmonary sporotrichosis, itraconazole 200 mg twice daily is recommended, with a total duration of therapy generally of 3 to 6 months based upon overall clinical response.
	• In patients with severe pulmonary sporotrichosis, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed or until a cumulative dose of 1 to 2 g of amphotericin B is reached, followed by itraconazole 200 mg twice daily, with total duration of therapy generally of 3 to 6 months based upon overall clinical response.
	<u>Blastomycosis (Immunocompetent Hosts)</u>
	• In patients with mild to moderate pulmonary blastomycosis, oral itraconazole 200 mg twice daily is recommended for 6 months.
	• In patients with severe pulmonary blastomycosis, amphotericin B 0.7–1.0 mg/kg/day daily is recommended until clinical improvement is observed, followed by continuation of amphotericin B 0.7–1.0 mg/kg three times weekly, until a cumulative dose of 1.5–2.5 g is reached. Once clinical improvement is observed, oral itraconazole 200 mg twice daily is recommended for 6 months.
	• In patients with pulmonary blastomycosis and bone involvement, it is recommended to prolong treatment with itraconazole to 12 months.
	• In patients with pulmonary blastomycosis and concomitant CNS involvement, the following are recommended:
	  o Liposomal amphotericin B 0.7 mg/kg/day until a cumulative dose of 2 g is reached
	  o Triazoles should not used as monotherapy for meningeal blastomycosis
	  o High dose intravenous or oral fluconazole 400–800 mg daily may be provided as an add-on therapy to intravenous amphotericin B in patients with severe or refractory disease, with the total duration of fluconazole therapy extended for at least 6 months.
	<u>Blastomycosis (Immunocompromised Hosts)</u>
	• In patients with severe pulmonary blastomycosis without CNS involvement, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed. Once clinical improvement is observed, oral itraconazole 200 mg twice daily is recommended for at least 12 months.
	• In patients with mild to moderate pulmonary blastomycosis without CNS involvement, oral itraconazole 200 mg twice daily is recommended for at least 12 months.
	• When AIDS is involved, oral itraconazole 200 mg/day is recommended indefinitely or until immunity is fully restored.

Clinical Guideline	Recommendation(s)

	• In patients with pulmonary blastomycosis and concomitant CNS involvement, the following are recommended:
	  o Combined therapy with amphotericin B 0.7 mg/kg/day together with intravenous or oral fluconazole 400–800 mg daily from the onset until clinical improvement is observed.
	  o Use of fluconazole for at least 12 months total after discontinuation of combined intravenous treatment with amphotericin B and high-dose fluconazole.
	  o Use of liposomal amphotericin B rather than amphotericin B deoxycholate should be considered due to theoretic better CNS penetration.
	  o Triazoles are not used as monotherapy.
	  o Patients with AIDS should continue to receive oral fluconazole 400 mg per day indefinitely or until immunity is restored.
	• In patients with pulmonary blastomycosis with new or progressing CNS involvement despite amphotericin B monotherapy, the following are recommended:
	  o Combined therapy with liposomal amphotericin B 5 g/kg/day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day.
	  o Fluconazole is used for at least 6 months in immunocompetent d fluconazole is used for at least 6 months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole.
	  o Patients with AIDS receive oral fluconazole 400 mg daily indefinitely or until immunity is restored.
	• In critically ill patients with pulmonary blastomycosis, the following are recommended:
	  o Combined therapy with amphotericin B (0.7–1.0 mg/kg amphotericin B deoxycholate or 5 mg/kg daily liposomal amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day.
	  o Following the initial intravenous therapy, oral itraconazole is used for at least 6 months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and itraconazole.
	  o After initial therapy is complete, patients with AIDS should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored. Voriconazole 200 mg twice daily may be used as an alternative to itraconazole.
	• In patients with pulmonary blastomycosis with new or progressing CNS involvement despite amphotericin B monotherapy, the following are recommended:
	  o Combined therapy with liposomal amphotericin B 5 mg/kg/ day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day.
	  o Fluconazole is used for at least 6 months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole.
	  o Patients with AIDS receive oral fluconazole 400 mg daily indefinitely or until immunity is restored.
	  o Voriconazole 200 mg twice daily may be considered as an

Clinical Guideline	Recommendation(s)

	alternative to fluconazole, though extensive disease-specific data are currently lacking.
	• In critically ill patients with pulmonary blastomycosis, the following are recommended:
	  o Combined therapy with amphotericin B (0.7–1.0 mg/kg amphotericin B deoxycholate or 5 mg/kg daily liposomal amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day.
	  o Following the initial intravenous therapy, oral itraconazole is used for at least 6 months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and itraconazole.
	  o After initial therapy is complete, patients with AIDS should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored.
	  o Voriconazole 200 mg twice daily may be considered as an alternative to itraconazole, though this is based largely on in vitro sensitivities and limited case based data.
	<u>Coccidioidomycosis (Immunocompetent Hosts)</u>
	• In most immunocompetent patients with primary pulmonary coccidioidomycosis and no additional risk factors for dissemination, we suggest no antifungal treatment.
	• In immunocompetent patients with primary pulmonary coccidioidomycosis and moderate to severe symptoms, or those in whom symptoms persist for more than 6 weeks, treatment with triazole antifungal drugs are recommended for at least 3 to 6 months or longer if symptoms and radiographic abnormalities persist.
	<u>Coccidioidomycosis (Immunocompromised Hosts and Others at Risk for Disseminated Disease)</u>
	• In many patients with pulmonary coccidioidomycosis and pulmonary nodules only, observation is recommended for at least 1 year without antifungal treatment. However, fluconazole (400 mg/d) or itraconazole (400 mg/d) may be considered during periods of significant immune suppression (i.e., chemotherapy, systemic corticosteroid therapy, or CD4 counts, 250/ml).
	• In patients with pulmonary coccidioidomycosis and pulmonary nodules who have additional risk factors for disseminated disease, patients with cavities, and those presenting with hemoptysis, treatment with triazole antifungal drugs are recommended, either fluconazole (400 mg/d) or itraconazole (400 mg/d).
	• For diffuse pulmonary coccidioidomycosis with significant impairment of gas exchange, initial liposomal amphotericin B (5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d) is recommended until clinical improvement, followed by fluconazole (400 mg/d) or itraconazole (400 mg/d) for at least another year. In patients with ongoing immune suppression, azole therapy may be continued indefinitely.
	• All patients, whether immunocompetent or immunocompromised, with any form of disseminated coccidioidomycosis require treatment. For non-meningeal disseminated disease, treatment with fluconazole (400 mg/d) or itraconazole (400 mg/d) is recommended for at least a year and until clinical improvement and stabilization. Itraconazole is preferred in bone disease. In severe or refractory cases, liposomal amphotericin B (5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d) may be initiated until clinical improvement, followed by fluconazole (400 mg/d) or itraconazole (400 mg/d) for at least another year.

Clinical Guideline	Recommendation(s)

	• In patients with meningitis, fluconazole (400–1,000 mg/d) or itraconazole (400–600 mg/d) for life. In patients with meningitis in whom treatment with triazole antifungal drugs failed, of intrathecal amphotericin B is recommended in select cases.
	<u>Paracoccidioidomycosis</u>
	• In critically ill patients with disseminated paracoccidioidomycosis, initial amphotericin B (0.7–1 mg/kg/d) therapy is recommended until clinical stabilization or until 2 g total dose administered. This may be followed by azole therapy as listed below.
	• In patients with disseminated paracoccidioidomycosis and mild to moderate or slowly progressive symptoms, one of the following options is recommended until clinical stabilization and resolution of symptoms. The total duration of therapy must be individualized to clinical response, but generally therapy for 6 to 12 months or longer is employed. Potential regimens include:
	  o Ketoconazole 200–400 mg daily
	  o Itraconazole 100–400 mg daily
	  o Sulfadiazine 4–6 g daily
	<u>Cryptococcosis (Immunocompetent Hosts)</u>
	• In asymptomatic immunocompetent patients with respiratory tract colonization by *C. neoformans*, no antifungal treatment is recommended.
	• In immunocompetent patients with pulmonary cryptococcosis and no evidence of other organ involvement, fluconazole 400 mg/day initially is recommended, tapering to 200 mg/day after clinical improvement is assured and with total treatment for 6 months. Alternatively, itraconazole 400 mg/day may be considered for 6 months. Fluconazole treatment is recommended for longer than 6 months in patients with documented *C. gattii* infection.
	<u>Cryptococcosis (Immunocompromised Hosts and Immunocompetent Hosts with Disseminated or CNS Involvement)</u>
	• In patients with disseminated cryptococcosis or CNS involvement, amphotericin B (0.7–1.0 mg/kg/d) plus flucytosine (100 mg/kg/d) is recommended for 2 weeks, then fluconazole or itraconazole (400 mg/d) for 8 to 10 weeks. Alternatively, amphotericin B (0.7–1.0 mg/kg/d) plus flucytosine (100 mg/kg/d) may be administered for 6 to 10 weeks in patients in whom azoles cannot be used.
	• In patients with disseminated cryptococcosis or CNS involvement, it is recommended that azoles not be used as monotherapy.
	• In patients with refractory disease not responding to fluconazole and itraconazole, voriconazole or posaconazole can be considered as salvage therapy on a case by case basis.
	• In patients with AIDS and CD4+ T cell count less than 200/ml who have disseminated cryptococcosis or CNS involvement, fluconazole 200 mg/day is recommended to be used indefinitely, after successful primary therapy as outlined above, or until CD4+ T cell count is greater than 200/ml, HIV RNA is undetectable and sustained for 3 months, and the patient is stable for 1 to 2 years.
	<u>Invasive Aspergillosis</u>
	• When invasive disease is suspected or confirmed, prompt, aggressive antifungal treatment is essential.
	• Although amphotericin B deoxycholate had historically been the ‘‘gold standard’’ for the treatment of invasive aspergillosis, most clinicians and the most recent IDSA guidelines recommend voriconazole as the primary treatment option.

Clinical Guideline	Recommendation(s)

	• There are no definitive data or consensus opinions indicating improved efficacy of any of the lipid amphotericin formulations over amphotericin B deoxycholate in the treatment of invasive aspergillosis. Thus, the best indication for using a lipid formulation appears to be for reducing renal toxicity to allow the administration of high doses of amphotericin for a prolonged time.
	• Voriconazole has recently emerged as a standard therapy for the treatment of invasive aspergillosis, based on the results of a randomized trial comparing the outcomes to amphotericin B deoxycholate; however, whether outcomes are superior to lipid formulations of amphotericin B has not been determined. In many instances voriconazole may be considered the treatment of choice the patient can be transitioned to oral formulations of this drug.
	• Oral itraconazole is not recommended for initial therapy for invasive aspergillosis. However, after disease progression is arrested with either voriconazole or amphotericin, the patient can be transitioned to oral itraconazole.
	• Caspofungin use in invasive aspergillosis is largely limited to salvage therapy, often in combination with other antifungal agents, after primary therapy with amphotericin-based regimens have failed.
	• There is currently insufficient clinical support to recommend combination therapy, although many clinicians are employing this approach as a ‘‘last option,’’ or in settings of particularly advanced disease.
	<u>Aspergillomas</u>
	• In patients with aspergillomas, it is recommended that antifungal agents not be used.
	• Antifungals should only be used only in patients suspected of having a component of semi-invasive disease.
	<u>Hypersensitivity Pneumonitis Related to *Aspergillus*</u>
	• In patients with hypersensitivity pneumonitis, it is recommended that antifungal therapy not be used.
	<u>Invasive Pulmonary Aspergillosis</u>
	• In patients with invasive pulmonary aspergillosis, the following are recommended:
	  o Intravenous voriconazole 6 mg/kg every 12 hours for 1 day, followed by 4 mg/kg every 12 hours until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400–600 mg/day until resolution or stabilization of all clinical and radiographic manifestations OR
	  o Intravenous liposomal amphotericin B 3–5 mg/kg/day until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400–600 mg/day until resolution or stabilization of all clinical and radiographic manifestation
	• In patients with invasive pulmonary aspergillosis who have failed front line therapy and are requiring salvage therapy, the following are recommended:
	  o Intravenous caspofungin 70 mg on Day 1 and 50 mg/day intravenously thereafter, or intravenous micafungin 100– 150 mg/day until improvement, followed by oral voriconazole 200 mg every 12 hours or oral itraconazole 400–600 mg/day until resolution of disease OR
	  o Posaconazole 200 mg four times per day initially, then 400 mg twice daily orally after stabilization of disease

Clinical Guideline	Recommendation(s)

	<u>Chronic Necrotizing Aspergillosis</u>
	• In patients with chronic necrotizing aspergillosis, with mild to moderate disease, voriconazole (200 mg every 12 h) or itraconazole (400–600 mg/d) is recommended until resolution or stabilization of all clinical and radiographic manifestations.
	• If clinically severe, consider beginning therapy of chronic necrotizing aspergillosis with either liposomal amphotericin B or IV voriconazole as described above for invasive disease.
	• In select patients at high risk of invasive fungal infection, some anti-*Aspergillus* prophylaxis is warranted. Data support the use of posaconazole 200 mg orally three times daily until recovery from neutropenia and clinical remission is established. Other prophylaxis approaches have utilized itraconazole, micafungin, and inhaled liposomal amphotericin B.
	<u>Candidemia</u>
	• Candidemia should be treated with antifungal agents, selecting one of the following agents: fluconazole, an amphotericin B formulation, an echinocandin, voriconazole, or the combination regimen of fluconazole and amphotericin B.
	• For patients who are clinically stable and have not recently received azole therapy, the following are recommended:
	  o Fluconazole (400 mg/d or ~6 mg/kg/d) OR
	  o Caspofungin (70 mg loading dose day 1, then 50 mg/d) OR
	  o Micafungin (100 mg/d) OR
	  o Anidulafungin (200 mg on day 1, then 100 mg/d).
	• For patients who are clinically unstable and for whom identification of the *Candida* species in the blood is unknown, there is no definitive recommendation. Several options are available and include:
	  o Amphotericin B deoxycholate (0.6–1.0 mg/kg/d) or a lipid formulation of amphotericin B (3–5 mg/kg/d) OR
	  o High-dose fluconazole (800 mg/kg/d or z 12 mg/kg/d) OR
	  o Caspofungin (70 mg loading dose day 1, then 50 mg/d) OR
	  o Micafungin (100 mg/d) OR
	  o Anidulafungin (200 mg on day 1, then 100 mg/d) OR
	  o Voriconazole (6 mg/kg/12 h X 2, then 3 mg/kg/12 h) OR
	  o A combination regimen with fluconazole (800 mg/d) and amphotericin B (0.6– 1.0 mg/kg/d, for the first 5–6 d)
	• For *C. albicans* and also possibly *C. tropicalis*, the drugs of choice are fluconazole (400 mg/d), amphotericin B (0.6–1.0 mg/kg/d), and an echinocandin.
	• For *C. parapsilosis*, the drugs of choice are fluconazole (400 mg/d) or amphotericin B (0.6–1.0 mg/kg/d).
	• For *C. glabrata*, the drugs of choice are an echinocandin or amphotericin B. High-dose fluconazole (800 mg/d) may be a suitable alternative.
	• For *C. krusei*, the drugs of choice are an echinocandin or amphotericin B.
	• For *C. lusitaniae*, fluconazole is the preferred therapy.
	• Lipid formulations of amphotericin B are usually indicated for patients intolerant of, or refractory to, conventional antifungal therapy
	<u>Other Fungi</u>
	• In patients with zygomycosis, lipid formulations of amphotericin B are recommended at 5 mg/kg/day or amphotericin B deoxycholate at 0.7–1.0 mg/kg/day.
	• In patients who are intolerant of, or refractory to, amphotericin B,

Clinical Guideline	Recommendation(s)
	posaconazole 200 mg orally four times per day is recommended.
Infectious Diseases Society of America (IDSA): **Treatment of Aspergillosis[10] (2008)**	Invasive Pulmonary Aspergillosis • For primary treatment of invasive pulmonary aspergillosis, IV or oral voriconazole is recommended for most patients. For seriously ill patients, the parenteral formulation is recommended. • Liposomal amphotericin B (L-AMB) may be considered as alternative primary therapy in some patients. For salvage therapy, agents include lipid formulations of amphotericin (LFABs), posaconazole, itraconazole, caspofungin, or micafungin. • In the absence of a well-controlled, prospective clinical trial, routine administration of combination therapy for primary therapy is not routinely recommended. For salvage therapy, an additional antifungal agent might be added to current therapy, or combination antifungal drugs from different classes other than those in the initial regimen may be used. Tracheobronchial Aspergillosis • Voriconazole is recommended as initial therapy in the treatment of tracheobronchial aspergillosis. Chronic Necrotizing Pulmonary Aspergillosis (CNPA) • The greatest body of evidence regarding effective therapy supports the use of orally administered itraconazole. • Although voriconazole (and presumably posaconazole) is also likely to be effective, there is less published information available. Single-organ, Extrapulmonary Forms of Invasive Aspergillosis • Voriconazole is recommended for primary treatment of these uncommon manifestations of invasive aspergillosis. Aspergillosis of the CNS • The weight of evidence supports voriconazole as the primary recommendation for systemic antifungal therapy of CNS aspergillosis. • Itraconazole, posaconazole, or LFAB are recommended for patients who are intolerant or refractory to voriconazole. Invasive Sinonasal Aspergillosis • If the infection is known to be due to *Aspergillus* species, voriconazole should be initiated. Aspergillus Endocarditis, Pericarditis, and Myocarditis • Voriconazole has been successfully used in case reports and may be the preferred agent. • Because of the potential for recurrent infections following replacement of an infected prosthetic valve, strong consideration should be given to lifelong antifungal therapy with an antifungal triazole, such as oral voriconazole or posaconazole. *Aspergillus* Osteomyelitis and Septic Arthritis • Combined medical and surgical intervention is recommended, where feasible, for management of *Aspergillus* osteomyelitis and arthritis. • Although there is currently limited experience with voriconazole for treatment of *Aspergillus* osteomyelitis, voriconazole appears to be effective for this indication. • Historically, AMB has been used and would be appropriate therapy. *Aspergillus* Endophthalmitis and *Aspergillus* Keratitis • Following a diagnostic vitreal tap, IV AMB and, where appropriate, intravitreal AMB plus pars plana vitrectomy may be sight saving in *Aspergillus* endophthalmitis. • Voriconazole administered intravitreally or systemically is an alterative regimen. Management of *Aspergillus* keratitis requires emergency ophthalmologic intervention with ophthalmologic

Clinical Guideline	Recommendation(s)
	examination, topical antifungal therapy, and systemic antifungal therapy with AMB, voriconazole, or itraconazole. Cutaneous Aspergillosis • Therapy for secondary cutaneous lesions reflects that of disseminated infection, with systemic voriconazole recommended as primary therapy. • Alternative agents include L-AMB, posaconazole, itraconazole, or an echinocandin. *Aspergillus* Peritonitis • Removal of peritoneal dialysis catheter and intraperitoneal dialysis with AMB, in addition to IV administration of AMB, are recommended. • Itraconazole or an extended-spectrum azole (voriconazole or posaconazole) may be used as a salvage therapy. Esophageal and Gastrointestinal Aspergillosis • Once a diagnosis is established, medical and, where appropriate, surgical therapy is needed to prevent the complications of potentially fatal hemorrhage, perforation, obstruction, and infarction. • Systemic antifungal therapy, as used for disseminated invasive aspergillosis, is appropriate. Hepatic Aspergillosis • Medical therapy of hepatic aspergillosis should be considered as initial therapy. • For extrahepatic or perihepatic biliary obstruction, surgical intervention is warranted. Empirical Antifungal Therapy of Neutropenic Patients • Empirical antifungal therapy with AMB, an LFAB, itraconazole, voriconazole, or caspofungin is recommended for high-risk patients with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy. Prophylaxis Against Invasive Aspergillosis • Antifungal prophylaxis with posaconazole can be recommended in HSCT recipients with GVHD who are at high risk for invasive aspergillosis and in patients with acute myelogenous leukemia or myelodysplastic syndrome who are at high risk for invasive aspergillosis. • Itraconazole may be effective, but tolerability limits its use. Aspergilloma and Chronic Pulmonary Aspergillosis • Antifungal chemotherapy with itraconazole, voriconazole, or presumably, posaconazole provides some potential for therapeutic benefit with comparatively minimal risk. *Aspergillus* Otomycosis (Otic Aspergillosis) • Topical therapy with irrigating solutions of boric acid, acetic acid, or azole cream may be effective in eradicating *Aspergillus* otomycosis. • For refractory cases and in contexts of perforated tympanic membranes, use of voriconazole, posaconazole, or itraconazole may be appropriate. Allergic Bronchopulmonary Aspergillosis • Treatment of allergic bronchopulmonary aspergillosis (APBA) should consist of a combination of corticosteroids and itraconazole. Allergic *Aspergillus* Sinusitis • Itraconazole is recommended for consideration in allergic *Aspergillus* sinusitis.

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Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for the Management of Blastomycosis[11] (2008)**	<u>Pulmonary Blastomycosis</u> • For moderately severe to severe disease, initial treatment with a lipid formulation of amphotericin B (AmB) at a dosage of 3–5 mg/kg per day or AmB deoxycholate at a dosage of 0.7–1 mg/kg per day for 1–2 weeks or until improvement is noted, followed by oral itraconazole, 200 mg 3 times per day for 3 days and then 200 mg twice per day, for a total of 6–12 months, is recommended. • For mild to moderate disease, oral itraconazole, 200 mg 3 times per day for 3 days and then once or twice per day for 6–12 months, is recommended. <u>Disseminated Extrapulmonary Blastomycosis</u> • For moderately severe to severe disease, lipid formulation AmB, 3–5 mg/kg per day, or AmB deoxycholate, 0.7–1 mg/kg per day, for 1–2 weeks or until improvement is noted, followed by oral itraconazole, 200 mg 3 times per day for 3 days and then 200 mg twice per day for a total of at least 12 months, is recommended. • For mild to moderate disease, oral itraconazole, 200 mg 3 times per day for 3 days and then once or twice per day for 6–12 months, is recommended. • Patients with osteoarticular blastomycosis should receive a total of at least 12 months of antifungal therapy. • Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure. <u>CNS Blastomycosis</u> • AmB, given as a lipid formulation at a dosage of 5 mg/kg per day over 4–6 weeks followed by an oral azole, is recommended. Possible options for azole therapy include fluconazole, 800 mg per day, itraconazole, 200 mg 2 or 3 times per day, or voriconazole, 200–400 mg twice per day, for at least 12 months and until resolution of CSF abnormalities. <u>Treatment for Immunosuppressed Patients with Blastomycosis</u> • AmB, given as a lipid formulation, 3–5 mg/kg per day, or AmB deoxycholate, 0.7–1 mg/kg per day, for 1–2 weeks or until improvement is noted, is recommended as initial therapy for patients who are immunosuppressed, including those with AIDS. • Itraconazole, 200 mg 3 times per day for 3 days and then twice per day, is recommended as step-down therapy after the patient has responded to initial treatment with AmB and should be given to complete a total of at least 12 months of therapy. • Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure. • Lifelong suppressive therapy with oral itraconazole, 200 mg per day, may be required for immunosuppressed patients if immunosuppression cannot be reversed and in patients who experience relapse despite appropriate therapy. <u>Treatment for Blastomycosis in Pregnant Women and in Children</u> • During pregnancy, lipid formulation AmB, 3–5 mg/ kg per day, is recommended. Azoles should be avoided because of possible teratogenicity. • If the newborn shows evidence of infection, treatment is recommended with AmB deoxycholate, 1.0 mg/kg per day. • For children with severe blastomycosis, AmB deoxycholate, 0.7–1.0 mg/kg per day, or lipid formulation AmB, at a dosage of 3–5 mg/kg

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	per day, is recommended for initial therapy, followed by oral itraconazole, 10 mg/kg per day (up to 400 mg per day) as step-down therapy, for a total of 12 months. • For children with mild to moderate infection, oral itraconazole, at a dosage of 10 mg/kg per day (to a maximum of 400 mg orally per day) for 6–12 months, is recommended. • Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for the Management of Candidiasis[12] (2009)**	<u>Candidemia in Non-neutropenic Patients</u> • Fluconazole or an echinocandin (caspofungin, micafungin or anidulafungin) is recommended as initial therapy for most adult patients. An echinocandin is recommended for patients with moderately severe to severe illness or for patients who have had recent azole exposure. Fluconazole is recommended for patients who are less critically ill and who have had no recent azole exposure. The same therapeutic approach is advised for children, with attention to differences in dosing regimens. • Transition from an echinocandin to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *Candida albicans*) and who are clinically stable. • For infection due to *Candida glabrata,* an echinocandin is preferred. Transition to fluconazole or voriconazole therapy is not recommended without confirmation of isolate susceptibility. For patients who have initially received fluconazole or voriconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of an azole to completion of therapy is reasonable. • For infection due to *Candida parapsilosis,* treatment with fluconazole is recommended. For patients who have initially received an echinocandin, are clinically improved, and whose follow-up culture results are negative, continuing use of an echinocandin is reasonable. • Amphotericin B deoxycholate (AmB-d) or a lipid formulation of AmB (LFAmB) are alternatives if there is intolerance to or limited availability of other antifungals. Transition from AmB-d or LFAmB to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *C. albicans*) and who are clinically stable. • Voriconazole is effective for candidemia, but it offers little advantage over fluconazole and is recommended as stepdown oral therapy for selected cases of candidiasis due to *Candida krusei* or voriconazole-susceptible *C. glabrata*. <u>Empirical Treatment for Suspected Invasive Candidiasis in Non-neutropenic Patients</u> • Empirical therapy for suspected candidiasis in non-neutropenic patients is similar to that for proven candidiasis. Fluconazole, caspofungin, anidulafungin, or micafungin is recommended as initial therapy. <u>Candidemia in Neutropenic Patients</u> • An echinocandin (caspofungin, micafungin or anidulafungin) or LFAmB is recommended for most patients. • For patients who are less critically ill and who have no recent azole exposure, fluconazole is a reasonable alternative. Voriconazole can be used in situations in which additional mold coverage is desired. • For infections due to *C. parapsilosis,* fluconazole or LFAmB is preferred as initial therapy. If the patient is receiving an echinocandin,

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	is clinically stable, and follow-up culture results are negative, continuing the echinocandin until completion of therapy is reasonable. For infections due to *C. krusei*, an echinocandin, LFAmB, or voriconazole is recommended. <u>Empirical Treatment for Suspected Invasive Candidiasis in Neutropenic Patients</u> • LFAmB, caspofungin, or voriconazole are recommended. • Fluconazole and itraconazole are alternative agents. • Azoles should not be used for empirical therapy in patients who have received an azole for prophylaxis. <u>Treatment for Neonatal Candidiasis</u> • AmB-d is recommended for neonates with disseminated candidiasis. If urinary tract involvement is excluded, LFAmB can be used. Fluconazole is a reasonable alternative. The recommended length of therapy is 3 weeks. • Echinocandins should be used with caution and are generally limited to situations in which resistance or toxicity precludes the use of fluconazole or AmB-d. • In nurseries with high rates of invasive candidiasis, fluconazole prophylaxis may be considered in neonates whose birth weight is <1000 g. Antifungal drug resistance, drug-related toxicity, and neurodevelopmental outcomes should be observed. <u>Urinary Tract Infections – Asymptomatic Candiduria</u> • Treatment is not recommended unless the patient belongs to a group at high risk of dissemination. Elimination of predisposing factors often results in resolution of candiduria. • High-risk patients include neutropenic patients, infants with low birth weight, and patients who will undergo urologic manipulations. Neutropenic patients and neonates should be managed as described for invasive candidiasis. For those patients undergoing urologic procedures, fluconazole or AmB-d for several days before and after the procedure is recommended. <u>Urinary Tract Infections – Symptomatic Candiduria</u> • For candiduria with suspected disseminated candidiasis, treatment as described for candidemia is recommended. • For cystitis due to a fluconazole-susceptible *Candida* species, oral fluconazole for 2 weeks is recommended. For fluconazole-resistant organisms, AmB-d for 1–7 days or oral flucytosine for 7–10 days are alternatives. AmB-d bladder irrigation is generally not recommended but may be useful for treatment of patients with fluconazole-resistant *Candida* species, especially *C. glabrata*. • For pyelonephritis due to fluconazole-susceptible organisms, oral fluconazole daily for 2 weeks is recommended. For patients with fluconazole-resistant *Candida* strains, especially *C. glabrata*, alternatives include AmB-d with or without flucytosine or flucytosine alone for 2 weeks. • For fungus balls, surgical intervention is strongly recommended in non-neonates. Fluconazole is recommended. AmB-d with or without flucytosine is an alternative. If access to the renal collecting system is available, an adjunct to systemic therapy is irrigation with AmB-d. Treatment duration should be until symptoms have resolved and urine cultures no longer yield *Candida* species. <u>Vulvovaginal Candidiasis (VVC)</u> • Several topical antifungal agents are effective therapy for VVC, and no agent is clearly more effective than another.

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	• A single 150-mg dose of fluconazole is recommended for the treatment of uncomplicated *Candida* VVC. • For recurring *Candida* VVC, 10–14 days of induction therapy with a topical or oral azole, followed by fluconazole once per week for 6 months, is recommended. <u>Chronic Disseminated Candidiasis</u> • Fluconazole is recommended for clinically stable patients. LFAmB or AmB-d can be used to treat acutely ill patients or patients with refractory disease. Induction therapy with AmB for 1–2 weeks, followed by oral fluconazole is also recommended. • Anidulafungin, micafungin, or caspofungin are alternatives for initial therapy, followed by oral fluconazole when clinically appropriate. • Therapy should be continued for weeks to months, until calcification occurs or lesions resolve. Premature discontinuation of antifungal therapy can lead to recurrent infection. • Patients with chronic disseminated candidiasis who require ongoing chemotherapy or undergo stem cell transplantation should continue to receive antifungal therapy throughout the period of high risk to prevent relapse. <u>Osteoarticular Candida Infections</u> • For osteomyelitis, fluconazole at a dosage of 400 mg daily for 6–12 months or LFAmB at a dosage of 3–5 mg/kg daily for at least 2 weeks, followed by fluconazole at a dosage of 400 mg daily for 6–12 months is recommended. Alternatives include an echinocandin or AmB-d at a dosage of 0.5–1 mg/kg daily for at least 2 weeks, followed by fluconazole at a dosage of 400 mg daily for 6–12 months. • For septic arthritis, treatment for at least 6 weeks with fluconazole at a dosage of 400 mg daily or LFAmB at a dosage of 3–5 mg/kg daily for at least 2 weeks, followed by fluconazole at a dosage of 400 mg daily is recommended. Alternatives include an echinocandin or AmB-d at a dosage of 0.5–1 mg/kg daily for at least 2 weeks, followed by fluconazole at a dosage of 400 mg daily for the remainder of therapy. • For infection involving a prosthetic device, device removal is recommended for most cases. Therapy for at least 6 weeks with the above dosages of fluconazole, LFAmB, an echinocandin, or AmB-d is recommended. If the device cannot be removed, chronic suppression with fluconazole is recommended. <u>Central Nervous System Candidiasis</u> • LFAmB with or without flucytosine is recommended for the initial several weeks of treatment. • Fluconazole is recommended as step-down therapy after the patient responds to initial treatment with LFAmB and flucytosine. Therapy should continue until all signs and symptoms, CSF abnormalities, and radiologic abnormalities have resolved. <u>Candida Endophthalmitis</u> • AmB-d combined with flucytosine is recommended for advancing lesions or lesions threatening the macula. Fluconazole is an acceptable alternative for less severe endophthalmitis. LFAmB, voriconazole, or an echinocandin can be used to treat patients who are intolerant of or experiencing treatment failure with AmB-d in combination with flucytosine or fluconazole. • The recommended duration of therapy is at least 4–6 weeks and is determined by the stabilization or resolution of lesions as documented by repeated ophthalmological examinations. <u>Cardiovascular Candida Infections</u>

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	• For native valve endocarditis, LFAmB with or without flucytosine is recommended. Alternatives include AmB-d with or without flucytosine or an echinocandin (caspofungin or anidulafungin). Step-down therapy to fluconazole should be considered among patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. Valve replacement is recommended, and treatment should continue for at least 6 weeks after valve replacement and should continue for a longer duration in patients with perivalvular abscesses and other complications. • For patients who cannot undergo valve replacement, long-term suppression with fluconazole is recommended. • For prosthetic valve endocarditis (PVE), the recommendations above apply, and suppressive therapy should be indefinite if valve replacement is not possible. • For pericarditis, LFAmB, AmB-d, an echinocandin, or fluconazole for as long as several months, in combination with either a pericardial window or pericardiectomy, is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to AmB or an echinocandin and who are clinically stable. • For myocarditis, treatment as for endocarditis (as stated above) is recommended. • For suppurative thrombophlebitis, catheter removal and incision and drainage or resection of the vein, if feasible, is recommended. LFAmB, AmB-d, fluconazole, or an echinocandin for at least 2 weeks after candidemia has cleared is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to AmB or an echinocandin and who are clinically stable. Resolution of the thrombus can be used as evidence to discontinue antifungal therapy if clinical and culture data are supportive. • For pacemaker and implantable cardiac defibrillator wire infections, removal of the entire device and systemic antifungal therapy with LFAmB with or without flucytosine, AmB-d with or without flucytosine, or an echinocandin is recommended. Step-down therapy to fluconazole should be considered for patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. For infections limited to generators and/or pockets, 4 weeks of antifungal therapy after removal of the device is recommended. For pacemaker and implantable cardiac defibrillator wire infections, at least 6 weeks of antifungal therapy after wire removal is recommended. • For ventricular assist devices that cannot be removed, treatment with LFAmB, AmB-d, or an echinocandin is recommended. After candidemia has cleared and the patient has responded clinically, fluconazole is recommended as step-down therapy. Chronic suppressive therapy with fluconazole is warranted until the device is removed. <u>Esophageal Candidiasis</u> • Systemic antifungal therapy is always required. Oral fluconazole for 14–21 days is recommended. Intravenous fluconazole, AmB-d, or an echinocandin should be used for patients who cannot tolerate oral therapy. A diagnostic trial of antifungal therapy is appropriate before performing an endoscopic examination. • For fluconazole-refractory disease, itraconazole solution, posaconazole suspension, or voriconazole (administered intravenously or orally) for 14– 21 days is recommended. Micafungin, anidulafungin or AmB-d are acceptable alternatives.

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	• Suppressive therapy with fluconazole is recommended for recurrent infections. • In patients with AIDS, treatment with HAART is recommended to reduce recurrent infections. Oropharyngeal Candidiasis • For mild disease, clotrimazole troches, nystatin suspension, or nystatin pastilles for 7–14 days is recommended. • For moderate to severe disease, oral fluconazole for 7–14 days is recommended. • For fluconazole-refractory disease, either itraconazole solution or posaconazole suspension for up to 28 days is recommended. Voriconazole or AmB-d is recommended when treatment with other agents has failed. Intravenous echinocandin or AmB-d can be used in treating patients with refractory disease. • Chronic suppressive therapy is usually unnecessary for patients with HIV infection. If suppressive therapy is required, fluconazole 3 times weekly is recommended. Treatment with HAART is recommended to reduce recurrent infections. Antifungal Prophylaxis for Solid-Organ Transplant Recipients, Patients Hospitalized in Intensive Care Units (ICUs), Neutropenic Patients receiving Chemotherapy, and Stem Cell Transplant Recipients at Risk of Candidiasis • For solid-organ transplant recipients, fluconazole or liposomal AmB (L-AmB) is recommended as postoperative antifungal prophylaxis for liver, pancreas, and small bowel transplant recipients at high risk of candidiasis. • For patients hospitalized in the ICU, fluconazole is recommended for high-risk patients in adult units that have a high incidence of invasive candidiasis. • For patients with chemotherapy-induced neutropenia, fluconazole, posaconazole, or caspofungin is recommended during induction chemotherapy for the duration of neutropenia. Oral itraconazole is an effective alternative, but it offers little advantage over other agents and is less well tolerated. • For stem cell transplant recipients with neutropenia, fluconazole, posaconazole, or micafungin is recommended during the period of risk of neutropenia.
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Treatment of Coccidioidomycosis[13] (2005)**	Uncomplicated Acute Coccidioidal Pneumonia • Commonly prescribed therapies include oral azole antifungal agents at dosages of 200–400 mg per day. Courses of therapy are typically administered for 3 to 6 months. • During pregnancy, amphotericin B is the treatment of choice because fluconazole (and likely other azole antifungals) are teratogenic. Diffuse Pneumonia • Therapy is usually begun either with amphotericin B or high-dose fluconazole. • Amphotericin B is more frequently used as initial therapy if significant hypoxia is present or if deterioration is rapid. • Several weeks of therapy are often required to produce clear evidence of improvement. After this time, amphotericin B therapy may be discontinued and replaced with treatment with an oral azole antifungal. • In combination, the total length of therapy should be at least 1 year, and for patients with severe immunodeficiency, oral azole therapy should be continued as secondary prophylaxis. Symptomatic Pulmonary Cavity Infections • Complications of coccidioidal cavities include local discomfort,

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	superinfection with other fungi or possibly bacteria, or hemoptysis. Should these complications occur, oral therapy with azole antifungals may result in improvement, although recurrence of symptoms may occur on cessation of therapy. • Rupture of a coccidioidal cavity into the pleural space, resulting in a pyopneumothorax, is an infrequent but serious complication of coccidioidal pneumonia. In young, otherwise-healthy patients, surgical closure by lobectomy with decortication is the preferred management. • Antifungal therapy is recommended for treatment, particularly in cases with delay of diagnosis and coexistent diseases. • For patients in whom the diagnosis was delayed a week or more, or for patients in whom there are coexistent diseases, management approaches are less uniform and may include courses of therapy with amphotericin B or oral azole antifungal drugs prior to surgery or chest tube drainage without surgery. <u>Chronic Progressive Fibrocavitary Pneumonia</u> • Initial treatment with oral azole antifungal agents is recommended. • If the patient improves sufficiently, therapy should be continued for at least 1 year. If therapy is not satisfactory, switching to an alternative azole antifungal, raising the dosage of the azole, or therapy with amphotericin B are alternative strategies. <u>Non-meningeal Disseminated Infection (Extrapulmonary)</u> • Initial therapy is usually initiated with oral azole antifungal agents. • Amphotericin B is recommended for alternative therapy, especially if lesions are appearing to worsen rapidly and are in particularly critical locations, such as the vertebral column. • In patients experiencing failure of conventional deoxycholate amphotericin B therapy, or experiencing intolerable drug-related toxicities, lipid amphotericin B formulations have been demonstrated to be safe and to cause less nephrotoxicity and may be considered. • Combination therapy with amphotericin B and an azole has been administered to some patients, especially when infection is widespread or in cases in which there has been disease progression during treatment with a single agent. Although combination therapy may improve responses, there is no evidence that such an approach is more effective than treatment with a single agent. <u>Meningeal Disseminated Infection (Extrapulmonary)</u> • Therapy with oral fluconazole is preferred by most clinicians. Itraconazole, administered in dosages of 400–600 mg per day, has also been reported to be comparably effective. • Some physicians also initiate therapy with intrathecal amphotericin B in addition to an azole on the basis that responses are more prompt with this approach. Patients who respond to azole therapy should continue this treatment indefinitely. Patients who do not respond to fluconazole or itraconazole would be candidates for intrathecal amphotericin B therapy with or without continuation of azole treatment.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for the Management of Cryptococcal Disease**[14] **(2010)**	<u>Cryptococcal Meningoencephalitis (HIV-Infected Individuals)</u> • Primary therapy: induction and consolidation: ○ Amphotericin B (AmB) deoxycholate (AmBd) (0.7–1.0 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses; IV formulations may be used in severe cases and in those without oral intake where the preparation is available) for at least 2 weeks, followed by fluconazole (400 mg [6 mg/kg] per day orally) for a minimum of 8 weeks.

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	○ Lipid formulations of AmB (LFAmB), including liposomal AmB (3–4 mg/kg per day IV) and AmB lipid complex (ABLC) (5 mg/kg per day IV) for at least 2 weeks, could be substituted for AmBd among patients with or predisposed to renal dysfunction. • Alternative regimens for induction and consolidation (listed in order of highest recommendation top to bottom): ○ AmBd (0.7–1.0 mg/kg per day IV), liposomal AmB (3–4 mg/kg per day IV), or ABLC (5 mg/kg per day IV) for 4–6 weeks. Liposomal AmB has been given safely at 6 mg/kg per day IV in cryptococcal meningoencephalitis and could be considered in the event of treatment failure or high–fungal burden disease. ○ AmBd (0.7 mg/kg per day IV) plus fluconazole (800 mg per day orally) for 2 weeks, followed by fluconazole (800 mg per day orally) for a minimum of 8 weeks. ○ Fluconazole (≥800 mg per day orally; 1200 mg per day is favored) plus flucytosine (100 mg/kg per day orally) for 6 weeks. ○ Fluconazole (800–2000 mg per day orally) for 10–12 weeks; a dosage of ≥1200 mg per day is encouraged if fluconazole alone is used. ○ Itraconazole (200 mg twice per day orally) for 10–12 weeks, although use of this agent is discouraged. <u>Non-Meningeal, Pulmonary Cryptococcosis (Immunosuppressed):</u> • For mild-to-moderate symptoms, absence of diffuse pulmonary infiltrates, absence of severe immunosuppression, and negative results of a diagnostic evaluation for dissemination, use fluconazole (400 mg [6 mg/kg] per day orally) for 6–12 months. • In HIV-infected patients who are receiving HAART with a CD4 cell count >100 cells/µL and a cryptococcal antigen titer that is ≤1:512 and/or not increasing, consider stopping maintenance fluconazole after 1 year of treatment. <u>Cryptococcal Meningoencephalitis (Non–HIV-Infected, Non-transplant Hosts)</u> • AmBd (0.7–1.0 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for at least 4 weeks for induction therapy. The 4-week induction therapy is reserved for persons with meningoencephalitis without neurological complications and cerebrospinal fluid (CSF) yeast culture results that are negative after 2 weeks of treatment. For AmBd toxicity issues, LFAmB may be substituted in the second 2 weeks. In patients with neurological complications, consider extending induction therapy for a total of 6 weeks, and LFAmB may be given for the last 4 weeks of the prolonged induction period. Then, start consolidation with fluconazole (400 mg per day) for 8 weeks. • If patient is AmBd intolerant, substitute liposomal AmB (3–4 mg/kg per day IV) or ABLC (5 mg/kg per day IV). • If flucytosine is not given or treatment is interrupted, consider lengthening AmBd or LFAmB induction therapy for at least 2 weeks. • In patients at low risk for therapeutic failure, consider induction therapy with combination of AmBd plus flucytosine for only 2 weeks, followed by consolidation with fluconazole (800 mg [12 mg/kg] per day orally) for 8 weeks. • After induction and consolidation therapy, use maintenance therapy with fluconazole (200 mg [3 mg/kg] per day orally) for 6–12 months.

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	Non-Meningeal, Pulmonary Cryptococcosis (Non-Immunosuppressed): • For mild-to-moderate symptoms, administer fluconazole (400 mg per day orally) for 6–12 months; persistently positive serum cryptococcal antigen titers are not criteria for continuance of therapy. • For severe disease, treat similarly to CNS disease. • Itraconazole (200 mg twice per day orally), voriconazole (200 mg twice per day orally), and posaconazole (400 mg twice per day orally) are acceptable alternatives if fluconazole is unavailable or contraindicated. Organ Transplant Recipients • For central nervous system (CNS) disease, liposomal AmB (3–4 mg/kg per day IV) or ABLC (5 mg/kg per day IV) plus flucytosine (100 mg/kg per day in 4 divided doses) for at least 2 weeks for the induction regimen, followed by fluconazole (400–800 mg [6–12 mg/kg] per day orally) for 8 weeks and by fluconazole (200–400 mg per day orally) for 6–12 months. If induction therapy does not include flucytosine, consider LFAmB for at least 4–6 weeks of induction therapy, and liposomal AmB (6 mg/kg per day) might be considered in high–fungal burden disease or relapse. • For mild-to-moderate non-CNS disease, fluconazole (400 mg [6 mg/kg] per day) for 6–12 months. • For moderately severe–to-severe non-CNS or disseminated disease without CNS involvement, treat the same as CNS disease. • In the absence of any clinical evidence of extrapulmonary or disseminated cryptococcosis, severe pulmonary disease is treated the same as CNS disease. For mild-to-moderate symptoms without diffuse pulmonary infiltrates, use fluconazole (400 mg [6 mg/kg] per day) for 6–12 months. • Fluconazole maintenance therapy should be continued for at least 6–12 months. Cryptococcal Meningoencephalitis (Management of Complications - Persistence) • Reinstitute induction phase of primary therapy for longer course (4–10 weeks). • Consider increasing the dose if the initial dosage of induction therapy was ≤0.7 mg/kg IV of AmBd per day or ≤3 mg/kg of LFAmB per day, up to 1 mg/kg IV of AmBd per day or 6 mg/kg of liposomal AmB per day; in general, combination therapy is recommended. • If the patient is polyene intolerant, consider fluconazole (≥800 mg per day orally) plus flucytosine (100 mg/kg per day orally in 4 divided doses). • If patient is flucytosine intolerant, consider AmBd (0.7 mg/kg per day IV) plus fluconazole (800 mg [12 mg/kg] per day orally). • Use of intrathecal or intraventricular AmBd is generally discouraged and is rarely necessary. Cerebral Cryptococcomas • Induction therapy with AmBd (0.7–1 mg/kg per day IV), liposomal AmB (3–4 mg/kg per day IV), or ABLC (5 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for at least 6 weeks. • Consolidation and maintenance therapy with fluconazole (400–800 mg per day orally) for 6–18 months. Non-Meningeal, Non-Pulmonary Cryptococcosis • If CNS disease is ruled out, fungemia is not present, infection occurs at single site, and there are no immunosuppressive risk factors, consider

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	fluconazole (400 mg [6 mg/kg] per day orally) for 6–12 months.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for the Management of Patients with Histoplasmosis**[15] **(2007)**	<u>Moderately Severe to Severe Acute Pulmonary Histoplasmosis (Adults)</u> • Lipid formulation of amphotericin B (3.0–5.0 mg/kg daily intravenously for 1–2 weeks) followed by itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily, for a total of 12 weeks) is recommended. <u>Mild-to-Moderate Acute Pulmonary Histoplasmosis (Adults)</u> • Treatment is usually unnecessary. Itraconazole (200 mg 3 times daily for 3 days and then 200 mg once or twice daily for 6–12 weeks) is recommended for patients who continue to have symptoms for 11 month. <u>Acute Pulmonary Histoplasmosis (Children)</u> • Treatment indications and regimens are similar to those for adults, except that amphotericin B deoxycholate (1. mg/kg daily) is usually well tolerated, and the lipid preparations are not preferred. • Itraconazole dosage in children is 5.0–10.0 mg/kg daily in 2 divided doses (not to exceed 400 mg daily), generally using the solution formulation. <u>Chronic Cavitary Pulmonary Histoplasmosis</u> • Itraconazole (200 mg 3 times daily for 3 days and then once or twice daily for at least 1 year) is recommended, but some prefer 18–24 months in view of the risk for relapse. • Blood levels of itraconazole should be obtained after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure. <u>Pericarditis</u> • Nonsteroidal anti-inflammatory therapy is recommended in mild cases. • Prednisone (0.5–1.0 mg/kg daily [maximum, 80 mg daily] in tapering doses over 1–2 weeks) is recommended for patients with evidence of hemodynamic compromise or unremitting symptoms after several days of therapy with nonsteroidal anti-inflammatory therapy. • Pericardial fluid removal is indicated for patients with hemodynamic compromise. • Itraconazole (200 mg 3 times daily for 3 days and then once or twice daily for 6–12 weeks) is recommended if corticosteroids are administered. <u>Rheumatologic Syndromes</u> • Nonsteroidal anti-inflammatory therapy is recommended in mild cases. • Prednisone (0.5–1.0 mg/kg daily [maximum, 80 mg daily] in tapering doses over 1–2 weeks) is recommended in severe cases. • Itraconazole (200 mg 3 times daily for 3 days and then once or twice daily for 6–12 weeks) is recommended only if corticosteroids are administered. <u>Mediastinal Lymphadenitis</u> • Treatment is usually unnecessary. Itraconazole (200 mg 3 times daily for 3 days and then 200 mg once or twice daily for 6–12 weeks) is recommended in patients who have symptoms that warrant treatment with corticosteroids and in those who continue to have symptoms for 11 month. • Prednisone (0.5–1.0 mg/kg daily [maximum, 80 mg daily] in tapering doses over 1–2 weeks) is recommended in severe cases with obstruction or compression of contiguous structures. <u>Mediastinal Granuloma</u> • Treatment is usually unnecessary. Itraconazole (200 mg 3 times daily for 3 days and then once or twice daily for 6–12 weeks) is

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	recommended for symptomatic cases. Mediastinal Fibrosis • Antifungal treatment is not recommended. The placement of intravascular stents is recommended for selected patients with pulmonary vessel obstruction. • Itraconazole (200 mg once or twice daily for 12 weeks) is recommended if clinical findings cannot differentiate mediastinal fibrosis from mediastinal granuloma. Progressive Disseminated Histoplasmosis (Adults) • For moderately severe to severe disease, liposomal amphotericin B (3.0 mg/kg daily) is recommended for 1–2 weeks, followed by oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of at least 12 months). • For mild-to-moderate disease, itraconazole (200 mg 3 times daily for 3 days and then twice daily for at least 12 months) is recommended. • Lifelong suppressive therapy with itraconazole (200 mg daily) may be required in immunosuppressed patients if immunosuppression cannot be reversed and in patients who relapse despite receipt of appropriate therapy. • Blood levels of itraconazole should be obtained to ensure adequate drug exposure. Progressive Disseminated Histoplasmosis (Children) • Amphotericin B deoxycholate (1.0 mg/kg daily for 4– 6 weeks) is recommended. • Amphotericin B deoxycholate (1.0 mg/kg daily for 2– 4 weeks) followed by itraconazole (5.0–10.0 mg/kg daily in 2 divided doses) to complete 3 months of therapy is an alternative. • Longer therapy may be needed for patients with severe disease, immunosuppression, or primary immunodeficiency syndromes. • Lifelong suppressive therapy with itraconazole (5.0 mg/kg daily, up to 200 mg daily) may be required in immunosuppressed patients if immunosuppression cannot be reversed and in patients who experience relapse despite receipt of appropriate therapy. • Blood levels of itraconazole should be obtained to ensure adequate drug exposure. Prophylaxis for Immunosuppressed Patients • Prophylaxis with itraconazole (200 mg daily) is recommended in patients with HIV infection with CD4 cell counts <150 cells/mm3 in specific areas of endemicity where the incidence of histoplasmosis is 110 cases per 100 patient-years. • Prophylaxis with itraconazole (200 mg daily) may be appropriate in specific circumstances in other immunosuppressed patients. CNS Histoplasmosis • Liposomal amphotericin B (5.0 mg/kg daily for a total of 175 mg/kg given over 4–6 weeks) followed by itraconazole (200 mg 2 or 3 times daily) for at least 1 year and until resolution of CSF abnormalities, including *Histoplasma* antigen levels, is recommended. • Blood levels of itraconazole should be obtained to ensure adequate drug exposure.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for the Management of Sporotrichosis[16] (2007)**	Lymphocutaneous and Cutaneous Sporotrichosis • For cutaneous and lymphocutaneous sporotrichosis, itraconazole 200 mg orally daily is recommended to be given for 2–4 weeks after all lesions have resolved, usually for a total of 3–6 months. • Patients who do not respond should be given a higher dosage of itraconazole (200 mg twice daily); terbinafine, administered at a

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	dosage of 500 mg orally twice daily; or saturated solution of potassium iodide (SSKI), initiated at a dosage of 5 drops (using a standard eye-dropper) 3 times daily and increasing, as tolerated, to 40–50 drops 3 times daily. • Fluconazole (400–800 mg daily) should be used only if the patient cannot tolerate these other agents. <u>Osteoarticular Sporotrichosis</u> • Itraconazole, administered at 200 mg orally twice daily for at least 12 months, is recommended. • Amphotericin B, given as a lipid formulation at a dosage of 3–5 mg/kg daily, or amphotericin B deoxycholate, administered at a dosage of 0.7–1.0 mg/kg daily, can be used for initial therapy. After the patient has shown a favorable response, therapy can be changed to itraconazole administered at a dosage of 200 mg orally twice daily to complete a total of at least 12 months of therapy. • Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure. <u>Pulmonary Sporotrichosis</u> • For severe or life-threatening pulmonary sporotrichosis, amphotericin B, given as a lipid formulation at 3–5 mg/kg daily, is recommended. Amphotericin B deoxycholate, administered at a dosage of 0.7–1.0 mg/kg daily, could also be used. • After the patient has shown a favorable response to amphotericin B, therapy can be changed to itraconazole (200 mg orally twice daily) to complete a total of at least 12 months of therapy. • For less severe disease, itraconazole administered at 200 mg orally twice daily for at least 12 months is recommended. • Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure. • Surgery combined with amphotericin B therapy is recommended for localized pulmonary disease. <u>Meningeal Sporotrichosis</u> • Amphotericin B, given as a lipid formulation at a dosage of 5 mg/kg daily for 4–6 weeks, is recommended for the initial treatment of meningeal sporotrichosis. Amphotericin B deoxycholate, administered at a dosage of 0.7–1.0 mg/kg daily, could also be used but was not preferred by the panel. • Itraconazole (200 mg twice daily) is recommended as step-down therapy after the patient responds to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of therapy. • Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure. • For patients with AIDS and other immunosuppressed patients, suppressive therapy with itraconazole at a dosage of 200 mg daily is recommended to prevent relapse. <u>Disseminated (Systemic) Sporotrichosis</u> • Amphotericin B, given as a lipid formulation at a dosage of 3–5 mg/kg daily, is recommended for disseminated sporotrichosis (B-III). Amphotericin B deoxycholate (0.7–1.0 mg/kg daily) could also be used but was not preferred by the panel. • Itraconazole (200 mg twice daily) is recommended as step-down

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	therapy after the patient responds to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of therapy. • Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure. • Lifelong suppressive therapy with itraconazole (200 mg daily) may be required for patients with AIDS and other immunosuppressed patients if immunosuppression cannot be reversed. <u>Sporotrichosis in Pregnant Women and in Children</u> • Amphotericin B, given as a lipid formulation at a dosage of 3–5 mg/kg daily, or amphotericin B deoxycholate, given at a dosage of 0.7–1 mg/kg daily, is recommended for severe sporotrichosis that must be treated during pregnancy; azoles should be avoided. • Itraconazole, administered at a dosage of 6–10 mg/kg to a maximum of 400 mg orally daily, is recommended for children with cutaneous or lymphocutaneous sporotrichosis. • For children with disseminated sporotrichosis, amphotericin B (0.7 mg/kg daily) should be the initial therapy, followed by itraconazole (6–10 mg/kg, up to a maximum of 400 mg daily) as step-down therapy.
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[17] (2008)**	<u>Aspergillosis</u> • Voriconazole is the drug of choice but should be used cautiously with HIV protease inhibitors and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. <u>Candidiasis (Mucocutaneous)</u> • Oral fluconazole is as effective as topical therapy for oropharyngeal candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral solution for 7–14 days is as effective as oral fluconazole but less well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. IV amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used. • Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14–21-day course of either fluconazole (oral or IV) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although IV caspofungin or IV voriconazole are effective in treating esophageal candidiasis among HIV-infected patients, oral or IV fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. • Vulvovaginal candidiasis in HIV-infected women is usually uncomplicated (90%) and responds readily to short-course oral or

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	topical treatment with any of several therapies, including oral fluconazole, topical azoles, and itraconazole oral solution. Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days. Coccidioidomycosis • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped. Cryptococcosis • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the CSF but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a 2-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for 8 weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. Histoplasmosis • Patients with moderately severe to severe disseminated histoplasmosis should be treated with an IV lipid formulation of amphotericin B for ≥2 weeks or until they clinically improve followed by oral itraconazole (200 mg three times daily for 3 days and then 200 mg twice daily for a total of ≥12 months. • In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for 3 days followed by 200 mg twice daily is appropriate initial therapy. Leishmaniasis • Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in HIV-coinfected patients. The optimal amphotericin B dosage has not been determined. • Regimens with efficacy include conventional amphotericin B 0.5–1.0 mg/kg body weight/day IV to achieve a total dose of 1.5–2.0 grams, or liposomal or lipid complex preparations of 2–4 mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1–5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20–60 mg/kg body weight. A higher daily dosage is

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	recommended for liposomal or lipid complex preparations than for conventional amphotericin B.
National Comprehensive Cancer Network (NCCN): **Prevention and Treatment of Cancer-Related Infections**[20] **(2011)**	Initial Therapy for Fever and Neutropenia • Fluconazole may be used as an addition to initial empiric broad-spectrum antibiotics if patients present with thrush. • Voriconazole or posaconazole may be used if refractory to fluconazole. Empiric Antifungal Therapy in Persistent Neutropenic Fever • Fluconazole has been used successfully as empiric therapy for neutropenic fever in patients not receiving prophylaxis but is limited by a lack of activity against molds. • Itraconazole in the capsule formulation has erratic bioavailability and is therefore not suitable as empiric antifungal therapy. • Voriconazole is an option for empiric therapy in patients at high risk for invasive mold infection. Prophylaxis in Cancer Patients with an Intermediate to High Overall Infection Risk • Consider fluconazole during neutropenia and for anticipated mucositis. • Patients with ALL may use fluconazole until resolution of neutropenia. • Patients with acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS) may use posaconazole or voriconazole until resolution of neutropenia. • Patients undergoing autologous hematopoietic stem cell transplant (HSCT) with mucositis may use fluconazole until resolution of neutropenia. • Patients undergoing allogeneic HSCT may use fluconazole, itraconazole, voriconazole, or posaconazole during neutropenia and for at least 75 days after transplant. • Patients with significant graft-versus-host disease (GVHD) may use posaconazole or voriconazole until resolution of significant GVHD. Miscellaneous Recommendations • Voriconazole is standard of care as primary therapy for invasive aspergillosis. • Data on posaconazole as primary therapy for invasive fungal infections are limited.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer**[18] **(2010)**	Antifungal Therapy in High Risk Patients • Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 4–7 days of antibiotics and whose overall duration of neutropenia is expected to be >7 days. • Data are insufficient to recommend a specific empirical antifungal agent for a patient already receiving antifungal prophylaxis, but switching to a different class of antifungals that is given intravenously should be considered. • Preemptive antifungal management is acceptable as an alternative to empirical antifungal therapy in a subset of high-risk neutropenic patients. Those who remain febrile after 4–7 days of broad-spectrum antibiotics but are clinically stable, have no clinical or chest and sinus computed tomography (CT) signs of fungal infection, have negative serologic assay results for evidence of invasive fungal infection, and have no recovery of fungi from any body site may have antifungal agents withheld. Antifungal therapy should be instituted if any of these indicators of possible invasive fungal infection are identified. • Prophylaxis against *Candida* infection is recommended in patient groups in whom the risk of invasive candidal infection is substantial, such as allogeneic hematopoietic stem cell transplant (HSCT)

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	recipients or those undergoing intensive remission-induction or salvage-induction chemotherapy for acute leukemia. Fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin are all acceptable alternatives. • Prophylaxis against invasive *Aspergillus* infections with posaconazole should be considered for selected patients >13 years of age who are undergoing intensive chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) in whom the risk of invasive aspergillosis without prophylaxis is substantial. <u>Antifungal Therapy Low Risk Patients</u> • In low-risk patients, the risk of invasive fungal infection is low, and therefore routine use of empirical antifungal therapy is not recommended. • Antifungal prophylaxis is not recommended for patients in whom the anticipated duration of neutropenia is >7 days.
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**[19] **(2009)**	• Fluconazole is the drug of choice for the prophylaxis of invasive candidiasis before engraftment in allogeneic HCT recipients, and may be started from the beginning or just after the end of the conditioning regimen. • The optimal duration of fluconazole prophylaxis is not defined. • Fluconazole is not effective against *C krusei* and *C glabrata* and should not be used for prophylaxis against these strains. • Micafungin is an alternative prophylactic agent. • Itraconazole oral solution has been shown to prevent invasive fungal infections, but use of this drug is limited by poor tolerability and toxicities. • Voriconazole and posaconazole may be used for prevention of candidiasis post-engraftment. • Oral amphotericin B, nystatin, and clotrimazole troches may control superficial infection and control local candidiasis but have not been shown to prevent invasive candidiasis. • Transplant patients with candidemia or candidiasis may still receive transplants if their infection is diagnosed early and treated aggressively with amphotericin B or appropriate doses of fluconazole. • Autologous recipients have a lower risk of infection compared to allogeneic recipients and may not require prophylaxis, though it is still recommended in patients who have underlying hematologic malignancies, those who will have prolonged neutropenia and mucosal damage, or have recently received fludarabine. Itraconazole oral solution has been shown to prevent mold infections. • In patients with GVHD, posaconazole has been reported to prevent invasive mold infections. • Patients with prior invasive aspergillosis should receive secondary prophylaxis with a mold-active drug. The optimal drug has not been determined, but voriconazole has been shown to have benefit for this indication.
European Academy of Dermatology and Venereology (EADV): **Onychomycosis Treatment Guidelines**[21] **(2005)**	• Prior to initiating treatment, it is important that diagnosis be confirmed and the etiological agent identified. • Topical monotherapy is indicated when the matrix area is not involved. Topical treatment is also suitable for patients who are reluctant to take oral medications or have swallowing difficulties. The only case in which it is not recommended is if nail penetration may be suboptimal. • Oral antifungal drugs are generally considered to be more effective than topical treatments. However, they are accompanied by a higher risk of systemic adverse effects and drug interactions.

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	• Oral monotherapy (terbinafine, itraconazole or fluconazole) or combined oral and topical (nail lacquer) is recommended when 1) at least 50% of the distal nail plate is involved; 2) the nail matrix area is involved; 3) mycological criteria such as the causative agent or agents are known and oral agents can target specific fungi; 4) topical drugs are not indicated when topical drug transport is suboptimal; and 5) oral or combined therapy is also recommended in cases of nail matrix area involvement. • Griseofulvin is associated with the poorest mycological cure rate (<30%) and is rarely used. Terbinafine is associated with the highest mycological cure rate (77–100%). • Combination therapy with systemic and topical treatments may be considered when a large portion of the nail plate is affected (>50%), when the nail matrix is involved, and in cases of treatment failure.
British Association of Dermatologists (BAD): **Guidelines for the Treatment of Onychomycosis[22] (2003)**	• Both topical and oral agents are available for the treatment of fungal nail infection. The primary aim of treatment is to eradicate the organism as demonstrated by microscopy and culture. • Systemic therapy is almost always more successful than topical treatment, which should only be used in superficial white onychomycosis (SWO), possibly very early distal and lateral subungual onychomycosis (DLSO) or when systemic therapy is contraindicated. • Both terbinafine and itraconazole have been shown to be more effective than griseofulvin in dermatophyte onychomycosis and therefore the optimum choice of treatment lies between terbinafine and itraconazole. • Terbinafine is more effective than itraconazole for dermatophyte infection of the nails and should be first-line treatment. Itraconazole may be considered a second-line treatment. • Expected cure rates vary and range from 80%-90% for fingernail infections and 70%-80% for toenail infections.
European Society for Pediatric Dermatology (ESPD): **Guidelines for the Management of Tinea Capitis in Children[140] (2010)**	• Tinea capitis always requires systemic treatment because topical antifungal agents do not penetrate the hair follicle. • Topical treatment is only used as adjuvant therapy to systemic antifungals. • Griseofulvin has been the gold standard for systemic therapy of tinea capitis. The main disadvantage of griseofulvin is the long duration of treatment required (6–12 weeks or longer) which may lead to reduced compliance. • The newer oral antifungal agents including terbinafine, itraconazole, and fluconazole appear to have efficacy rates and potential adverse effects similar to those of griseofulvin in children with tinea capitis due to *Trichophyton* species, while requiring much shorter duration of treatment. The decision between griseofulvin and newer antifungal agents for children with *Trichophyton* species can be based on the balance between duration of treatment and compliance. • Griseofulvin is still the treatment of choice for cases caused by *Microsporum* species. • Adjunctive topical therapies, such as selenium sulfide or ketoconazole shampoos, as well as fungicidal creams or lotions have been shown to decrease the carriage of viable spores responsible for the disease contagion and reinfection and may shorten the cure rate with oral antifungals. • The topical fungicidal cream/lotion should be applied to the lesions once daily for a week. The shampoo should be applied to the scalp and

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	hair for 5 minutes twice weekly for 2–4 weeks or three times weekly until the patient is clinically and mycologically cured. The latter in conjunction with 1 week of topical fungicidal cream or lotion application is recommended.

British Association of Dermatologists (BAD): **Guidelines for the Management of Tinea Capitis[23] (2000)**	• The aim of treatment is to achieve a clinical and mycological cure as quickly as possible.
	• Oral antifungal therapy is generally needed. Topical treatment alone is not recommended for the management of tinea capitis.
	• Oral therapy options include griseofulvin, terbinafine, itraconazole, fluconazole, and ketoconazole.
	• If there has been no clinical response and signs persist at the end of the treatment period, then the options include:
	  o Increase the dose or duration of the original drug (both griseofulvin and terbinafine have been used successfully and safely at higher doses or for longer courses to clear resistant infections)
	  o Change to an alternative antifungal (e.g. switch from griseofulvin to terbinafine or itraconazole).
	• Symptom-free carriers with light growth/low spore count on culture may be treated with twice weekly selenium or povidone shampoo.
	• The definitive end-point for adequate treatment is not clinical response but mycological cure; therefore, follow-up with repeat mycology sampling is recommended at the end of the standard treatment period and then monthly until mycological clearance is documented. Treatment should, therefore, be tailored for each individual patient according to response.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the azoles 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 Azoles[1-8]

Indication	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Aspergillosis (invasive)					✔
Aspergillosis in patients intolerant of or refractory to amphotericin B therapy		✔ †			
Blastomycosis		✔ †	✔		
Candida pneumonia	✔				
Candida wound infections					✔
Candidemia	✔				✔
Candidiasis			✔		
Candidiasis (abdominal)					✔
Candidiasis (bladder wall)					✔
Candidiasis (kidney)					✔
Candidiasis (Peritoneum)	✔				
Candidiasis (skin, disseminated)					✔
Candidiasis (disseminated)	✔				
Candidiasis (esophageal)	✔	✔ ‡			✔
Candidiasis (mucocutaneous)			✔		
Candidiasis (oropharyngeal)	✔	✔ ‡	✔	✔	

Indication	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Candidiasis (vaginal)	✔				
Candiduria	✔		✔		
Chromomycosis			✔		
Coccidioidomycosis			✔		
Cryptococcal meningitis	✔				
Histoplasmosis		✔ †	✔		
Onychomycosis of the fingernail		✔ †			
Onychomycosis of the toenail (with or without fingernail involvement)		✔ †			
Paracoccidioidomycosis			✔		
Prophylaxis of candidiasis in patients undergoing bone marrow transplantation receiving cytotoxic chemotherapy and/or radiation	✔				
Prophylaxis of invasive *Aspergillus* and *Candida* infections in severely immunocompromised patients				✔	
Recalcitrant cutaneous dermatophyte infections who have not responded to topical therapy or oral griseofulvin or who are unable to take oral griseofulvin			✔		
Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species in patients intolerant of or refractory to other therapy					✔

† Capsule formulation only
‡ Solution formulation only

IV. Pharmacokinetics

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

Table 5. Pharmacokinetic Parameters of the Azoles[1-8]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Fluconazole	Oral: >90	11-12	Liver	Renal (80)	30
Itraconazole	55-68	>99	Liver	Renal (40) Feces (3-18)	64
Ketoconazole	75	91-99	Liver	Feces (75) Renal (13)	2-12
Posaconazole	Variable	>98	Liver	Feces (71-77) Renal (13-14)	35
Voriconazole	96	58	Liver	Renal (>94)	Variable

V. Drug Interactions

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

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

Generic Name(s)	Significance Level	Interaction	Mechanism
Azoles (fluconazole,	1	Alfentanil, fentanyl,	The pharmacological adverse effects of the opioid analgesics

Generic Name(s)	Significance Level	Interaction	Mechanism
itraconazole, ketoconazole, voriconazole)		sufentanil	may be increased.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Cisapride	Increased cisapride plasma concentrations resulting in cardiotoxicity may occur.
Azoles (itraconazole, ketoconazole)	1	Conivaptan	Increased levels and adverse effects of conivaptan may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Crizotinib	May result in increased crizotinib concentrations and an increased risk of QT interval prolongation.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Dasatinib	May result in an increased risk of QT interval prolongation.
Azoles (itraconazole, ketoconazole)	1	Dofetilide	Increased levels and adverse effects of dofetilide may occur, including ventricular arrhythmias and torsades de pointes.
Azoles (voriconazole)	1	Efavirenz	Voriconazole concentrations may be decreased, decreasing therapeutic effects, and efavirenz concentrations may be increased, increasing the risk of side effects.
Azoles (itraconazole, ketoconazole)	1	Eplerenone	Increased eplerenone plasma concentrations may occur, increasing the risk of hyperkalemia and serious arrhythmias.
Azoles (itraconazole, ketoconazole, posaconazole, voriconazole)	1	Ergot derivatives	An increased risk of ergot toxicity has been observed.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Lapatinib	May result in increased lapatinib plasma concentrations and increased risk of QT interval prolongation.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Nilotinib	May result in increased nilotinib plasma concentrations and an increased risk of QT interval prolongation.
Azoles	1	Pimozide	The risk of life-threatening

Generic Name(s)	Significance Level	Interaction	Mechanism
(itraconazole, ketoconazole, posaconazole, voriconazole)			arrhythmias is increased.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Quetiapine	May result in increased quetiapine serum concentrations and an increased risk of QT prolongation.
Azoles (itraconazole, posaconazole, voriconazole)	1	Quinidine	Quinidine levels may be increased, increasing the risk of cardiovascular events.
Azoles (itraconazole, ketoconazole)	1	Ranolazine	Ranolazine levels may be increased, increasing the risk of QT prolongation, torsades de pointes, and sudden death.
Azoles (voriconazole)	1	Ritonavir	Therapeutic effect of voriconazole may be decreased.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Salmeterol	May result in increased salmeterol plasma concentrations and increased risk of QT interval prolongation.
Azoles (fluconazole, posaconazole, voriconazole)	1	Serotonin antagonists (ondansetron, granisetron)	May result in an increased risk of QT interval prolongation.
Azoles (fluconazole, posaconazole, voriconazole)	1	Sorafenib	May result in increased risk of QT interval prolongation and risk of ventricular arrhythmias.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Sparfloxacin	May result in an increased risk of QT interval prolongation and torsade de pointes.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Sunitinib	May result in an increased risk of QT interval prolongation.
Azoles (ketoconazole)	1	Taxoids	Increased levels and adverse effects of the taxoids may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Terfenadine	May result in increased serum concentrations of terfenadine and its active metabolite, and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).

Generic Name(s)	Significance Level	Interaction	Mechanism
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Vinblastine, vincristine	Vinca alkaloid toxicity may be increased when co-administered with azole antifungals.
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)	1	Warfarin	Anticoagulant effect of warfarin may be increased.
Azoles (itraconazole, ketoconazole)	2	Alfuzosin	Increased levels and adverse effects of alfuzosin may occur.
Azoles (fluconazole, itraconazole, ketoconazole)	2	Almotriptan, eletriptan	Increased levels and adverse effects of almotriptan and eletriptan may occur.
Azoles (ketoconazole)	2	Antacids	Therapeutic effects of ketoconazole may be decreased.
Azoles (itraconazole, ketoconazole)	2	Aripiprazole	Increased levels and adverse effects of aripiprazole may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	2	Benzodiazepines	Increased serum levels of benzodiazepines with CNS depression and psychomotor impairment is possible.
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)	2	Bosentan	Increased levels of bosentan and increased adverse effects may occur.
Azoles (fluconazole, itraconazole, ketoconazole)	2	Buspirone	Increased buspirone levels and increased adverse effects may occur.
Azoles (itraconazole)	2	Busulfan	Increased levels and adverse effects of busulfan may occur.
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)	2	Carbamazepine	Increased carbamazepine levels and increased adverse effects may occur.
Azoles (Posaconazole)	2	Cimetidine	Plasma concentrations and therapeutic effect of posaconazole may be decreased.
Azoles (itraconazole, ketoconazole)	2	Cimetidine, famotidine, nizatidine, ranitidine	Effects of itraconazole and ketoconazole may be attenuated.
Azoles (fluconazole, itraconazole, ketoconazole,	2	Corticosteroids	Corticosteroid effects and toxicity may be increased.

Generic Name(s)	Significance Level	Interaction	Mechanism
voriconazole)			
Azoles (fluconazole, itraconazole, ketoconazole)	2	Cyclophosphamide	Increased adverse effects of cyclophosphamide may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	2	Cyclosporine	Cyclosporine levels and toxicity may increase and persist more than 1 week after stopping antifungal therapy.
Azoles (itraconazole, ketoconazole)	2	Didanosine	Therapeutic effects of azole antifungals may be decreased.
Azoles (itraconazole)	2	Digoxin	Serum digoxin concentrations and adverse effects may be increased.
Azoles (itraconazole, ketoconazole, posaconazole, voriconazole)	2	Felodipine	Felodipine concentrations may be increased, leading to peripheral edema and adverse effects.
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)	2	Gefitinib	Increased gefitinib adverse reactions may occur.
Azoles (fluconazole, itraconazole, ketoconazole)	2	Haloperidol	Elevated haloperidol plasma concentrations and adverse effects may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	2	HMG-CoA reductase inhibitors	Increased plasma levels of HMG-CoA reductase inhibitors and rhabdomyolysis may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	2	Nisoldipine	Increased nisoldipine levels and adverse reactions may occur.
Azoles (fluconazole, voriconazole)	2	Nonsteroidal anti-inflammatory drugs (NSAIDs)	Elevated plasma concentrations of NSAIDs and increases in adverse reactions may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	2	Phenytoin	Increased phenytoin levels and toxicity may occur.
Azoles (itraconazole, ketoconazole, posaconazole, voriconazole)	2	Phosphodiesterase (PDE) 5 inhibitors	Increased levels and adverse effects of PDE5 inhibitors may occur.

Generic Name(s)	Significance Level	Interaction	Mechanism
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole)	2	Protease inhibitors	Increased levels and adverse effects of protease inhibitors may occur.
Azoles (itraconazole, ketoconazole)	2	Proton-pump inhibitors	Plasma levels of azole antifungals may be reduced, decreasing the therapeutic effect.
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)	2	Quetiapine	Increased levels and adverse effects of quetiapine may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole)	2	Rifamycins	Plasma levels of azole antifungals may be decreased, ketoconazole may interfere with rifamycin absorption, and itraconazole may inhibit rifabutin metabolism.
Azoles (fluconazole, itraconazole, ketoconazole)	2	Risperidone	Increased levels and adverse effects of risperidone may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	2	Sirolimus	Increased levels and adverse effects of sirolimus may occur.
Azoles (ketoconazole)	2	Solifenacin	Increased levels and adverse effects of solifenacin may occur.
Azoles (fluconazole, ketoconazole)	2	Sulfonylureas	Hypoglycemic effects of tolbutamide and glimepiride may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	2	Tacrolimus	Increased levels and adverse effects of tacrolimus may occur.
Azoles (fluconazole, itraconazole, ketoconazole)	2	Tolterodine	Tolterodine plasma concentrations may be elevated, increasing the pharmacologic and adverse effects of tolterodine.
Azoles (fluconazole, ketoconazole)	2	Tricyclic antidepressants	Increased levels and adverse effects of tricyclic antidepressants may occur, including cardiac arrhythmias.
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)	2	Venlafaxine	Venlafaxine levels may be elevated, leading to an increase in adverse effects.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the azoles are listed in Table 7. The boxed warning for itraconazole is listed in Table 8 and the boxed warning for ketoconazole is listed in Table 9.

Table 7. Adverse Drug Events (%) Reported with the Azoles[1-8]

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Cardiovascular System					
Atrial arrhythmia	-	-	-	-	<2
Atrial fibrillation	-	-	-	-	<2
Atrioventricular block	-	-	-	-	<2
Bigeminy	-	-	-	-	<2
Bradycardia	-	-	-	-	<2
Bundle branch block	-	-	-	-	<2
Cardiomegaly	-	-	-	-	<2
Cardiomyopathy	-	-	-	-	<2
Chest pain	-	3	-	-	<2
Congestive heart failure	-	✔	-	-	<2
Endocarditis	-	-	-	-	<2
Extrasystoles	-	-	-	-	<2
Hypertension	-	2-3	-	1-18	<2
Hypotension	-	1	-	14	<2
Myocardial infarction	-	-	-	-	<2
Nodal arrhythmia	-	-	-	-	<2
Orthostatic hypotension	-	1	-	-	-
Palpitation	-	-	-	-	<2
Phlebitis	-	-	-	-	<2
Postural hypotension	-	-	-	-	<2
QT prolongation	✔	-	✔	4	<2
Substernal chest pain	-	-	-	-	<2
Supraventricular extrasystoles	-	-	-	-	<2
Supraventricular tachycardia	-	-	-	-	<2
Syncope	-	-	-	-	<2
Tachycardia	-	1	-	12	2
Torsades de pointes	✔	-	-	✔	<2
Ventricular dysrhythmias	-	-	✔	-	<2
Ventricular fibrillation	-	-	-	-	<2
Ventricular tachycardia	-	-	-	-	<2
Central Nervous System					
Abnormal dreaming	-	2	-	-	<2
Acute brain syndrome	-	-	-	-	<2
Agitation	-	-	-	-	<2
Akathisia	-	-	-	-	<2
Amnesia	-	-	-	-	<2
Anxiety	-	3	-	9	<2
Asthenia	-	2	-	1-2	<2
Ataxia	-	-	-	-	<2
Brain edema	-	-	-	-	<2
Cerebral hemorrhage	-	-	-	-	<2
Cerebral ischemia	-	-	-	-	<2
Cerebrovascular accident	-	-	-	-	<2
Coma	-	-	-	-	<2
Confusion	-	-	-	-	<2
Convulsion	-	-	-	-	<2
Delirium	-	-	-	-	<2

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Dementia	-	-	-	-	<2
Depersonalization	-	-	-	-	<2
Depression	-	3	✔	-	<2
Diplopia	-	-	-	-	<2
Dizziness	1	1-4	<1	1-11	<2
Encephalitis	-	-	-	-	<2
Encephalopathy	-	-	-	-	<2
Euphoria	-	-	-	-	<2
Extrapyramidal syndrome	-	-	-	-	<2
Guillain-Barre syndrome	-	-	-	-	<2
Hallucinations	-	-	-	-	2
Headache	2-13	1-10	<1	1-8	3
Hypertonia	-	-	-	-	<2
Hypoesthesia	-	✔	-	-	<2
Insomnia	-	✔	-	1-17	<2
Intracranial hypertension	-	-	-	-	<2
Neuralgia	-	-	-	-	<2
Neuropathy	-	✔	-	-	<2
Nystagmus	-	-	-	-	<2
Oculogyric crisis	-	-	-	-	<2
Psychosis	-	-	-	-	<2
Seizures	✔	-	-	-	<2
Somnolence	-	1	<1	1	<2
Suicidal tendencies	-	-	✔	-	<2
Tremor	-	1-2	-	-	<2
Vertigo	-	1	-	-	<2
Dermatological					-
Alopecia	✔	✔	✔	-	<2
Cellulitis	-	-	-	-	✔
Contact dermatitis	-	-	-	-	<2
Discoid lupus erythematosus	-	-	-	-	<2
Dry skin	-	-	-	-	<2
Eczema	-	-	-	-	<2
Erythema multiforme	-	✔	-	-	✔
Erythematous rash	-	1-2	-	-	-
Exfoliative dermatitis	-	✔	-	-	<2
Fixed drug eruption	-	-	-	-	<2
Furunculosis	-	-	-	-	<2
Maculopapular rash	-	-	-	-	<2
Melanosis	-	-	-	-	<2
Petechiae	-	-	-	11	-
Photosensitivity skin reaction	-	✔	-	-	<2
Pruritus	✔	1-5	2	1-11	<2
Psoriasis	-	-	-	-	<2
Rash	2	3-9	-	1-19	5-7
Skin discoloration	-	-	-	-	<2
Skin disorder	-	2	-	-	<2
Stevens-Johnson syndrome	✔	✔	-	-	✔
Toxic epidermal necrolysis	✔	✔	-	-	✔
Urticaria	-	✔	✔	-	<2
Endocrine and Metabolic					
Adrenal insufficiency	-	✔	-	✔	<2
Dehydration	-	<2	-	1	-
Diabetes insipidus	-	-	-	-	<2

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Edema	-	2-4	-	9-15	<2
Erectile dysfunction	-	✔	-	-	-
Fluid overload	-	1	-	-	-
Gynecomastia	-	✔	<1	-	-
Male breast pain	-	✔	-	-	-
Menstrual disorder	-	✔	-	-	-
Weight loss	-	<2	-	1	-
Gastrointestinal					
Abdomen enlarged	-	-	-	-	<2
Abdominal pain	2-6	2-6	1	1-27	<2
Anorexia	-	1	-	1-15	<2
Appetite increased	-	2	-	-	-
Ascites	-	-	-	-	<2
Cheilitis	-	-	-	-	<2
Cholecystitis	-	-	-	-	<2
Cholelithiasis	-	-	-	-	<2
Cholestasis	✔	-	-	-	1
Constipation	-	1-3	-	1-21	<2
Diarrhea	2-3	3-11	<1	3-42	<2
Dry mouth	✔	-	-	1	<2
Duodenal ulcer perforation	-	-	-	-	<2
Duodenitis	-	-	-	-	<2
Dyspepsia	1	<2-4	-	1-10	<2
Dysphagia	-	<2	-	-	<2
Esophageal ulcer	-	-	-	-	<2
Esophagitis	-	-	-	-	<2
Flatulence	-	<2-4	-	1	<2
Gastritis	-	2	-	-	-
Gastroenteritis	-	2	-	-	<2
Gastrointestinal disorders	-	4	-	-	-
Gastrointestinal hemorrhage	-	-	-	-	<2
Gingivitis	-	-	-	-	<2
Glossitis	-	-	-	-	<2
Gum hemorrhage	-	-	-	-	<2
Gum hyperplasia	-	-	-	-	<2
Hematemesis	-	-	-	-	<2
Hemorrhoids	-	<2	-	-	-
Intestinal perforation	-	-	-	-	<2
Intestinal ulcer	-	-	-	-	<2
Melena	-	-	-	-	<2
Mouth ulceration	-	-	-	-	<2
Mucositis	-	-	-	2-17	-
Nausea	2-7	3-11	3	5-38	5
Pancreatitis	-	-	-	-	<2
Parotid gland enlargement	-	-	-	-	<2
Periodontitis	-	-	-	-	<2
Proctitis	-	-	-	-	<2
Pseudomembranous colitis	-	-	-	-	<2
Rectal disorder	-	-	-	-	<2
Rectal hemorrhage	-	-	-	-	<2
Stomach ulcer	-	-	-	-	<2
Stomatitis	-	-	-	-	<2
Taste loss	-	-	-	-	<2
Taste perversion	1	<2	-	1	<2

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Tongue edema	-	-	-	-	<2
Ulcerative stomatitis	-	3	-	-	-
Vomiting	2-5	5-7	3	4-29	4
Genitourinary					
Albuminuria	-	1	-	-	<2
Anuria	-	-	-	-	<2
Blighted ovum	-	-	-	-	<2
Creatinine clearance decreased	-	-	-	-	<2
Cystitis	-	3	-	-	-
Dysmenorrhea	-	-	-	-	<2
Dysuria	-	-	-	-	<2
Epididymitis	-	-	-	-	<2
Glycosuria	-	-	-	-	<2
Hematuria	-	<2	-	-	<2
Hemolytic uremic syndrome	-	-	-	✔	-
Hemorrhagic cystitis	-	-	-	-	<2
Hydronephrosis	-	-	-	-	<2
Impotence	-	1	<1	-	<2
Kidney function abnormal	-	1	-	-	<1
Kidney pain	-	-	-	-	<2
Kidney tubular necrosis	-	-	-	-	<2
Libido decreased	-	1	-	-	<2
Metrorrhagia	-	-	-	-	<2
Nephritis	-	-	-	-	<2
Nephrosis	-	-	-	-	<2
Oligospermia	-	-	<1	-	-
Oliguria	-	-	-	-	<2
Pelvic pain	-	-	-	-	<2
Pollakiuria	-	✔	-	-	-
Renal failure	-	-	-	1	<1
Scrotal edema	-	-	-	-	<2
Urinary incontinence	-	✔	-	-	<2
Urinary retention	-	-	-	-	<2
Urinary tract infection	-	3	-	-	<2
Uterine hemorrhage	-	-	-	-	<2
Vaginal hemorrhage	-	-	-	10	<2
Hematological					
Agranulocytosis	✔	-	-	-	<2
Anemia	-	-	-	2-25	<2
Aplastic anemia	-	-	-	-	<2
Bleeding time increased	-	-	-	-	<2
Cyanosis	-	-	-	-	<2
Disseminated intravascular coagulation	-	-	-	-	<2
Ecchymosis	-	-	-	-	<2
Eosinophilia	-	-	-	-	<2
Hemolytic anemia	-	-	<1	-	<2
Hypervolemia	-	-	-	-	<2
Leukopenia	✔	✔	<1	-	<2
Lymphadenopathy	-	-	-	-	<2
Lymphangitis	-	-	-	-	<2
Marrow depression	-	-	-	-	<2
Neutropenia	✔	✔	-	2-23	-
Pancytopenia	-	-	-	-	<2
Petechia	-	-	-	-	<2

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Purpura	-	-	-	-	<2
Splenomegaly	-	-	-	-	<2
Thrombocytopenia	✔	✔	<1	1-29	<2
Thrombotic thrombocytopenic purpura	-	-	-	✔	<2
Hepatic					
Hepatic coma	-	-	-	-	<2
Hepatic failure	✔	✔	-	-	<2
Hepatic function abnormal	-	3	<1	1	-
Hepatitis	✔	✔	-	1	<2
Hepatomegaly	-	-	-	-	<2
Hepatotoxicity	-	✔	-	-	-
Jaundice	✔	-	-	-	<2
Laboratory Test Abnormalities					
Alkaline phosphatase increased	✔	2-4	-	1-3	4
Bilirubinemia	-	6	-	1-10	<1
Blood urea nitrogen increased	-	1	-	-	<2
Creatinine increased	-	3	-	3	<1
Creatinine phosphokinase increased	-	-	-	-	<2
Hypercalcemia	-	-	-	-	<2
Hypercholesterolemia	✔	-	-	-	<2
Hyperglycemia	-	-	-	11	<2
Hyperkalemia	-	-	-	-	<2
Hypermagnesemia	-	-	-	-	<2
Hypernatremia	-	-	-	-	<2
Hyperthyroidism	-	-	-	-	<2
Hypertriglyceridemia	✔	3	✔	-	-
Hyperuricemia	-	-	-	-	<2
Hypocalcemia	-	1	-	9	<2
Hypoglycemia	-	-	-	-	<2
Hypokalemia	✔	2-9	-	1-30	2
Hypomagnesemia	-	2	-	18	<2
Hyponatremia	-	-	-	-	<2
Hypophosphatemia	-	1-2	-	-	<2
Hypothyroidism	-	-	-	-	<2
Lactate dehydrogenase increased	-	2	-	-	-
Transaminases increased	✔	✔	-	2-17	2-3
Uremia	-	-	-	✔	<2
Musculoskeletal					
Arthralgia	-	✔	-	11	<2
Arthritis	-	-	-	-	<2
Back pain	-	<2	-	10	<2
Bone necrosis	-	-	-	-	<2
Bone pain	-	-	-	-	<2
Bursitis	-	3	-	-	-
Leg cramps	-	-	-	-	<2
Malaise	✔	1-3	-	-	-
Musculoskeletal pain	-	-	-	16	-
Myalgia	✔	1-3	-	1	<2
Myasthenia	-	-	-	-	<2
Myopathy	-	-	-	-	<2
Osteomalacia	-	-	-	-	<2
Osteoporosis	-	-	-	-	<2
Respiratory					
Coughing	-	4	-	1-24	<2

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Dyspnea	-	1-2	-	1-20	<2
Epistaxis	-	-	-	14	<2
Hemoptysis	-	-	-	-	<2
Hypoxia	-	-	-	-	<2
Lung edema	-	-	-	-	<2
Pharyngitis	-	2	-	12	-
Pleural effusion	-	-	-	-	<2
Pneumonia	-	2	-	3	<2
Pulmonary edema	-	✔	-	-	-
Pulmonary embolus	-	-	-	✔	<2
Pulmonary infiltration	-	1-2	-	-	-
Respiratory disorder	-	-	-	-	<2
Respiratory distress syndrome	-	-	-	-	<2
Rhinitis	-	<2-9	-	-	<2
Sinusitis	-	2-7	-	-	<2
Sputum increased	-	2	-	-	-
Upper respiratory tract infection	-	<2-8	-	7	<2
Special Senses					
Abnormality of accommodation	-	-	-	-	<2
Blepharitis	-	-	-	-	<2
Blurred vision	-	✔	-	1	-
Conjunctivitis	-	-	-	-	<2
Corneal opacity	-	-	-	-	<2
Chromatopsia	-	-	-	-	1
Deafness	-	-	-	-	<2
Diplopia	-	✔	-	-	-
Dry eyes	-	-	-	-	<2
Ear pain	-	-	-	-	<2
Eye hemorrhage	-	-	-	-	<2
Eye pain	-	-	-	-	<2
Keratitis	-	-	-	-	<2
Mydriasis	-	-	-	-	<2
Night blindness	-	-	-	-	<2
Optic atrophy	-	-	-	-	<2
Optic neuritis	-	-	-	-	<2
Otitis externa	-	-	-	-	<2
Photophobia	-	-	<1	-	2
Retinitis	-	-	-	-	<2
Scleritis	-	-	-	-	<2
Tinnitus	-	✔	-	-	<2
Uveitis	-	-	-	-	<2
Visual disturbances	-	<2	-	-	19
Other					
Allergic reactions	-	✔	-	✔	<2
Anaphylactoid reaction	-	✔	-	-	✔
Anaphylaxis	✔	✔	-	-	-
Angioedema	✔	✔	-	-	<2
Angioneurotic edema	-	✔	-	-	-
Bacteremia	-	-	-	18	-
Bulging fontanelles	-	-	<1	-	-
Candidiasis, oral	-	-	-	1	-
Chills	-	-	<1	-	4
Cytomegalovirus infection	-	-	-	14	-
Facial edema	✔	-	-	-	<2

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Fatigue	✔	2-3	-	1-17	-
Fever	✔	2-7	<1	2-45	6
Flank pain	-	-	-	-	<2
Flu syndrome	-	-	-	-	<2
Gingivitis	-	3	-	-	-
Graft versus host disease	-	-	-	-	<2
Granuloma	-	-	-	-	<2
Herpes simplex	-	-	-	3-15	<2
Herpes zoster	-	2	-	-	-
Hot flashes	-	<2	-	-	-
Hypoacusis	-	-	-	-	<2
Implantation complication	-	<2	-	-	-
Increased intracranial pressure	-	-	✔	-	-
Infection	-	<2	-	-	<2
Injection site pain	-	-	-	-	<2
Injury	-	3-7	-	-	-
Mucous membrane disorder	-	-	-	-	<2
Multi organ failure	-	-	-	-	<2
Pain	-	2-3	-	1	<2
Papilledema	-	-	✔	-	<2
Paresthesia	-	✔	✔	✔	<2
Peripheral edema	-	✔	-	-	<2
Peritonitis	-	-	-	-	<2
Pneumocystis carinii infection	-	2	-	-	-
Rigors	-	1	-	<1-20	-
Sepsis	-	-	-	-	<2
Serum sickness	-	✔	-	-	-
Sweating	-	2-3	-	2	<2
Thrombophlebitis	-	-	-	-	<2
Vasculitis	-	1	-	-	-
Vasodilation	-	-	-	-	<2
Weakness	-	-	-	1-8	-

✔ Percent not specified
- Event not reported

Table 8. Boxed Warning for Itraconazole[1]

WARNING
Congestive Heart Failure: If signs or symptoms of CHF occur during administration of itraconazole, reassess continued itraconazole use. Do not administer itraconazole capsules for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as CHF or a history of CHF. If signs or symptoms of CHF occur during administration of itraconazole capsules, discontinue administration. When itraconazole was administered intravenously (IV) to dogs and healthy human volunteers, negative inotropic effects were seen. Drug interactions: Coadministration of cisapride, pimozide, quinidine, or dofetilide with itraconazole is contraindicated. Itraconazole, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, or quinidine concomitantly with itraconazole and/or other CYP3A4 inhibitors.

Table 9. Boxed Warning for Ketoconazole[1]

WARNING
Hepatotoxicity: When used orally, ketoconazole has been associated with hepatic toxicity, including some fatalities. Patients receiving this drug should be informed by the physician of the risk and should be closely monitored. Drug interactions: Terfenadine: Coadministration of terfenadine with ketoconazole tablets is contraindicated. Rare cases of serious cardiovascular adverse events, including death, ventricular tachycardia and torsades de pointes have been observed in patients taking ketoconazole tablets concomitantly with terfenadine, due to increased terfenadine concentrations induced by ketoconazole tablets. Astemizole: Pharmacokinetic data indicate that oral ketoconazole inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylastemizole which may prolong QT intervals. Coadministration of astemizole with ketoconazole tablets is therefore contraindicated. Cisapride: Coadministration of cisapride with ketoconazole is contraindicated. Serious cardiovascular adverse events including ventricular tachycardia, ventricular fibrillation and torsades de pointes have occurred in patients taking ketoconazole concomitantly with cisapride.

VII. Dosing and Administration

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

Table 10. Usual Dosing Regimens for the Azoles[1-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Fluconazole	Cryptococcal Meningitis: 400 mg on the first day, followed by 200 mg once daily for 10 to 12 weeks after the CSF becomes culture negative Esophageal Candidiasis: 200 mg on the first day, followed by 100 mg once daily. Treatment should be continued for at least 3 weeks, and for at least 2 weeks following resolution of symptoms Oropharyngeal Candidiasis: 200 mg on the first day, followed by 100 mg once daily. Treatment should be continued for at least 2 weeks to decrease the likelihood of relapse Prophylaxis in Patients Undergoing Bone Marrow Transplantation: 400 mg once daily starting several days before expected neutropenia and continuing for 7 days after the neutrophil	Cryptococcal Meningitis: 12 mg/kg on the first day, followed by 6 mg/kg once daily for 10-12 weeks after the CSF becomes culture negative Esophageal Candidiasis: 6 mg/kg on the first day, followed by 3 mg/kg once daily for at least 3 weeks, and for at least 2 weeks following resolution of symptoms Oropharyngeal Candidiasis: 6 mg/kg on the first day, followed by 3 mg/kg once daily for at least 2 weeks Systemic *Candida* Infections: Daily doses of 6-12 mg/kg/day have been used in an open, non-comparative study of a small number of children	Injection: 100 mg/50 ml 200 mg/100 ml 400 mg/200 ml Suspension: 10 mg/ml 40 mg/ml Tablet: 50 mg 100 mg 150 mg 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	count rises above 1,000 cells per cu mm Systemic *Candida* Infections: For systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia, optimal therapeutic dosage and duration of therapy have not been established. In open, non-comparative studies of small numbers of patients, doses of up to 400 mg daily have been used. Urinary Tract Infections and Peritonitis: 50 to 200 mg daily have been used in non-comparative studies with small numbers of patients Vaginal Candidiasis: Oral: 150 mg orally as a single dose		
Itraconazole	Aspergillosis: Capsule: 200 to 400 mg daily Blastomycosis and Histoplasmosis: Capsule: 200 mg once daily; may be increased by 100 mg increments to a total daily dose of 400 mg Esophageal Candidiasis: Solution: 100 mg daily for a minimum of 3 weeks. Treatment should continue for 2 weeks after the resolution of symptoms. Onychomycosis (Fingernails Only): Capsule: 2 treatment pulses, each consisting of 200 mg twice daily for 1 week. The pulses are separated by a 3-week period without itraconazole. Onychomycosis (Toenails With or Without Fingernail Involvement): Capsule: 200 mg once daily for	Safety and efficacy in children have not been established.	Capsule: 100 mg Solution: 10 mg/ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	12 consecutive weeks Oropharyngeal Candidiasis: Solution: 200 mg daily for 1-2 weeks. Oropharyngeal Candidiasis (Unresponsive/Refractory to Fluconazole): Solution: 100 mg twice daily for 2-4 weeks		
Ketoconazole	Fungal Infections: 200 mg once daily; maximum, 400 mg daily	Fungal Infections: >2 years of age: 3.3 to 6.6 mg/kg in a single daily dose	Tablet: 200 mg
Posaconazole	Oropharyngeal Candidiasis: 100 mg twice daily on day 1, then 100 mg once daily for 13 days Oropharyngeal Candidiasis (Refractory to Itraconazole and/or Fluconazole): 400 mg twice daily. Duration of therapy is based on clinical response. Prophylaxis of Invasive Fungal Infections: 200 mg 3 times daily. Duration of therapy is based on recovery from neutropenia and immunosuppression.	Oropharyngeal Candidiasis: ≥13 years of age: 100 mg twice daily on day 1, then 100 mg once daily for 13 days Oropharyngeal Candidiasis (Refractory to Itraconazole and/or Fluconazole): ≥13 years of age: 400 mg twice daily. Duration of therapy is based on clinical response. Prophylaxis of Invasive Fungal Infections: ≥13 years of age: 200 mg 3 times daily. Duration of therapy is based on recovery from neutropenia and immunosuppression.	Suspension: 200 mg/5 ml
Voriconazole	Candidemia in Nonneutropenic Patients and Other Deep Tissue *Candida* Infections: 6 mg/kg every 12 hours for the first 24 hours then 3 to 4 mg/kg IV every 12 hours. Patients may be switched to the oral formulation when indicated at a dose of 200 mg every 12 hours. Esophageal Candidiasis: 200 mg every 12 hours for 14 days, and at least 7 days following resolution of symptoms Invasive Aspergillosis and Serious Fungal Infections due to *Fusarium* Species and *Scedosporium apiospermum*; 6 mg/kg every 12 hours for the first 24 hours, then 4 mg/kg IV every 12 hours. Patients may	Candidemia in Nonneutropenic Patients and Other Deep Tissue *Candida* Infections: ≥13 years of age: 6 mg/kg every 12 hours for the first 24 hours then 3 to 4 mg/kg IV every 12 hours. Patients may be switched to the oral formulation when indicated at a dose of 200 mg every 12 hours. Esophageal Candidiasis: ≥13 years of age: 200 mg every 12 hours for 14 days, and at least 7 days following resolution of symptoms Invasive Aspergillosis and Serious Fungal Infections due to *Fusarium* Species and *Scedosporium apiospermum*; ≥13 years of age: 6 mg/kg every 12 hours for the first 24	Injection: 200 mg Suspension: 200 mg/5 ml Tablet: 50 mg 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	be switched to oral therapy when indicated at a dose of 200 mg every 12 hours.	hours, then 4 mg/kg IV every 12 hours. Patients may be switched to oral therapy when indicated at a dose of 200 mg every 12 hours.	

VIII. Effectiveness

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

Table 11. Comparative Clinical Trials with the Azoles

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aspergillosis				
Maertens et al.[24] (2006) Caspofungin 70 mg IV daily in combination with either an azole (itraconazole or voriconazole) or a polyene (amphotericin B deoxycholate or an amphotericin B lipid preparation) All patients received active treatment with combination therapy.	MC, OL Patients 16 years of age and older with definite or probable invasive aspergillosis refractory or intolerant to standard antifungal therapy (amphotericin B deoxycholate, lipid preparations of amphotericin B, caspofungin, itraconazole, voriconazole, or posaconazole)	N=53 12 months posttreatment follow-up	Primary: Clinical response (favorable= complete or partial response; complete response= resolution of all signs, symptoms, radiologic and/or bronchoscopic evidence; partial response= clinically meaningful improvement in the above measures)	Primary: At the end of combination therapy, 55% of patients had a favorable response. Of the patients with a favorable response (29), 4 showed a complete response and 25 showed a partial response. At day 84, 49% of patients had a favorable response. Success at the end of combination therapy ranged from 43% in the caspofungin plus itraconazole group to 60% in the caspofungin plus voriconazole group. In the caspofungin plus polyene group, success rates were 80%, 29%, and 50% for amphotericin B deoxycholate, amphotericin B lipid complex, and liposomal amphotericin B, respectively. Of 46 refractory patients, the addition of caspofungin to the initially refractory antifungal agent demonstrated a favorable response in 66% of patients. Success was observed in 20% of patients who were initially refractory to caspofungin and had a non-echinocandin antifungal agent added. Of the patients who were refractory to voriconazole therapy, 73% had a favorable response when caspofungin was added to voriconazole compared to a 40% favorable response rate in patients who discontinued voriconazole and switched to 2 new antifungal agents.
Caillot et al.[25] (2003) Itraconazole 200 mg IV every 12 hours for 2 days, 200 mg IV daily	MC, OL Patients ≥18 years of age with proven or probable active invasive pulmonary aspergillosis who	N=21 14 weeks or last day of treatment or neutropenia	Primary: Clinical response (complete= resolution of signs and symptoms and radiographic and bronchoscopic	Primary: Complete or partial response was observed in 47% and 90% of patients at weeks 2 and 14, respectively. Secondary: Overall, 62% of patients had a complete or partial response at any time point and 86% had a complete or partial response or stable disease (i.e.,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 12 days, then 200 mg orally twice daily for 12 weeks	were immuno-compromised and refractory to amphotericin B		abnormalities; partial=major improvement in above listed criteria without complete resolution) Secondary: Total number of patients responding, median time to achieve response, microbiological results from anterior nares and sputum	minor or no improvement in disease without deterioration) at any time point. The median time to achieve response was 14 days. At week 14, there were no positive cultures obtained.
Caillot et al.[26] (2001) Itraconazole 200 mg IV every 12 hours for 2 days, 200 mg IV daily for 12 days, then 200 mg orally twice daily for 12 weeks	MC, OL Patients 25-78 years of age with active invasive pulmonary aspergillosis and who were immuno-compromised	N=31 14 weeks	Primary: Clinical response Secondary: Median time to achieve response, microbiological results from anterior nares and sputum	Primary: Complete or partial response was observed in 32.3%, 38.7%, and 48% of patients at week 2, week 14 and at study end, respectively. Overall, 58% of patients experienced a complete or partial response at any time during the study. When stable disease was considered as a positive response, the success rate was 67.7% at day 14, 45.2% at the end of oral therapy, and 68% at the end of the study. A total of 87% of patients achieved a complete, partial, or stable response at any time during the study. Secondary: The median time to achieve global response was 55 days. At week 14, there were no positive cultures.
Raad et al.[123] (2008)	RCT Patients with	N=143 Up to 12	Primary: Response rate to salvage therapy	Primary: The overall response rate to salvage therapy was 40% for posaconazole, 8% for L-AMB (P≤0.001) and 11% for combination therapy (P<0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Posaconazole 800 mg/day in divided doses vs amphotericin B liposome 7.5 mg/kg/day (L-AMB) vs amphotericin B liposome 7.5 mg/kg/day plus caspofungin 70 mg on day 1, followed by 50–100 mg daily	hematologic malignancies and invasive aspergillosis enrolled in a compassionate-use trial of antifungal salvage therapy	weeks	Secondary: Deaths related to aspergillosis within 12 months after initiation of salvage therapy and adverse events	Secondary: Aspergillosis contributed to the death of 40% of posaconazole group, 65% of the L-AMB group and 68% of the combination group (P≤0.008). By multivariate analysis, posaconazole therapy independently improved response (95% CI, 2.8–32.5; P<0.001). L-AMB alone or in combination with caspofungin was associated with a significantly higher rate of nephrotoxicity (P≤0.02) and hepatotoxicity (P<0.03) than monotherapy with posaconazole.
Sambatakou et al.[27] (2006) Voriconazole 200 mg orally twice daily (with an increase to 250 mg twice daily based on response and tolerability) for 4-24 weeks	MC, OL Patients >18 years of age with definite or probable subacute invasive aspergillosis at different body sites or chronic pulmonary aspergillosis	N=36 12 week posttreatment follow-up	Primary: Clinical response	Primary: Response rates at the end of treatment in subacute invasive aspergillosis and chronic pulmonary aspergillosis patients were 43% and 80%, respectively.
Mouas et al.[28] (2005) Voriconazole 6 mg/kg IV every	RETRO Patients 4-78 years of age with definite or probable invasive	N=20 End of therapy (4-395 days)	Primary: Response at end of therapy	Primary: Overall response rates were similar in both treatment groups (55%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12 hours on day 1, followed by 4 mg/kg IV every 12 hours or 200 mg orally twice daily vs voriconazole 400 mg orally twice daily on day 1, then 200 mg twice daily	bone aspergillosis			
Herbrecht et al.[29] (2002) Voriconazole 6 mg/kg IV twice daily on day 1, followed by 4 mg/kg IV twice daily for ≥7 days, then 200 mg orally twice daily vs amphotericin B deoxycholate 1.0-1.5 mg/kg/day	RCT, DB, MC Immuno-compromised patients ≥12 years of age with definite or probable invasive aspergillosis	N=277 12 weeks	Primary: Clinical response Secondary: Response at end of initial therapy, safety outcomes, survival up to week 12	Primary: Successful response rates at week 12 in patients receiving voriconazole and amphotericin B deoxycholate were 52.8% and 31.6%, respectively, and were significantly better in the voriconazole group. Secondary: Successful response rates at end of initial therapy in patients receiving voriconazole and amphotericin B deoxycholate were 49.7% and 27.8%, respectively. There were significantly fewer adverse events in the voriconazole group compared to the amphotericin B group (P=0.02). Visual disturbances (44.8% vs 4.3%, P<0.001), chills and/or fever (3.1% vs 24.9%, P<0.001) and severe adverse events (13.4% vs 24.3%, P=0.008), including renal impairment (1.0% vs 10.3%, P<0.001), hypokalemia (0% vs 3.2%, P=0.01) and systemic events (0.5% vs 3.8%, P=0.03) occurred in patients receiving voriconazole and amphotericin B deoxycholate, respectively. The survival rates for patients receiving voriconazole and amphotericin B deoxycholate were70.8% and 57.9%, respectively.
Blastomycosis and Histoplasmosis				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wheat et al.[31] (1995) Itraconazole 300 mg orally twice daily for 3 days then 200 mg twice daily with meals for 12 weeks	MC, OL, PRO Patients 13 years of age and older with serologically documented HIV and first-episode disseminated histoplasmosis	N=59 12 weeks	Primary: Clinical response (resolution of signs and symptoms and clearance of positive cultures), clearance of positive cultures, drug tolerance Secondary: Effect of therapy on *H capsulatum* var *capsulatum* antigen levels	Primary: Clinical response was observed in 85% of patients. Fungemia cleared after a median of 1 week. Secondary: *H capsulatum* var *capsulatum* antigen levels cleared from the urine and serum at rates of 0.2 and 0.3 units per week, respectively. Initial antigen levels reverted to negative in serum and urine in 46% and 9% of patients, respectively (P<0.001). The mean reduction in antigen was significantly higher in serum compared to urine (3.7 units and 2.0 units respectively, P=0.032).
Dismukes et al.[32] (1992) Itraconazole 200 mg, 300 mg, or 400 mg daily	MC, RCT Patients 18 years of age and older with a diagnosis of histoplasmosis or blastomycosis	N=85 12 month posttreatment follow-up	Primary: Clinical response	Primary: Among patients with blastomycosis, 90% were reported as having clinical success. For patients treated for more than 2 months, the clinical success rate was 95%. Among patients with histoplasmosis, 81% were reported as having clinical success. For patients treated for more than 2 months, the clinical success rate was 86%.
Hecht et.al.[33] (1997) Itraconazole 200 mg orally daily vs itraconazole 400 mg orally daily	MC, OL, PRO Patients >13 years of age with first episode of mild-moderate disseminated histoplasmosis with human immunodeficiency virus (HIV) who had successfully completed induction itraconazole therapy	N=46 ≥52 weeks	Primary: Relapse of histoplasmosis, survival Secondary: Drug-limiting toxicity, change in serum and urine *Histoplasma* polysaccharide antigen levels	Primary: The relapse-free rate at one year for all patients was 95.3%. The survival rate for all patients at one year and at study completion was 73.0% and 41%, respectively. Secondary: Toxicity leading to withdrawal occurred in 8 of 46 patients. The median change in serum and urine antigen levels of all patients who did not relapse by end of maintenance therapy was a decrease of 0.2 units and 2.1 units, respectively (P=0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	for 12 weeks			
Wheat et al.[34] (2001) Itraconazole 300 mg orally twice daily for 3 days then 200 mg twice daily for 12 weeks vs amphotericin B liposomal 3 mg/kg/day IV for 2 weeks, followed by itraconazole 200 mg twice daily for 10 weeks	CS HIV-infected patients ≥13 years of age with a first episode of disseminated histoplasmosis	N=110 12 weeks	Primary: Mycological response (negative blood cultures), time to negative blood cultures	Primary: By the end of the second week of therapy, blood cultures were negative in over 85% of amphotericin B patients compared to 53% of itraconazole patients (P=0.0008). By 12 weeks of therapy, cultures were negative in all patients in both groups. After 2 weeks of therapy, serum antigen levels fell by a significantly greater amount in the amphotericin B group compared to the itraconazole group (P=0.02). After 2 weeks of treatment, serum antigen levels were negative in 28% of the amphotericin B group and 20% of the itraconazole group (P=0.55). After 2 weeks of therapy, urine antigen levels were below the detection limit in 19% of amphotericin B patients and 3% of itraconazole patients (P=0.06). After 2 weeks of therapy, urine antigen levels fell by a significantly greater amount in the amphotericin B group compared to the itraconazole group (P<0.0005). By 12 weeks of therapy, there was no significant difference in the proportion of patients with undetectable serum and urine antigen levels in either group (P<0.80).
Dismukes et al.[30] (1985) Ketoconazole 400 mg PO QD ≥6 months vs ketoconazole 800	MC, PRO, RCT Patients 17-80 years of age with presumptive or culture-proven blastomycosis or histoplasmosis	N=134 6 month posttreatment follow-up	Primary: Clinical response (cure=resolution or reduction in symptoms and signs in addition to resolution or 50% reduction in size of lesion and negative cultures;	Primary: Clinical response rates in blastomycosis patients receiving low- and high-dose ketoconazole were 70% and 85%, respectively (P=0.12). Clinical response rates in histoplasmosis patients receiving low- and high-dose ketoconazole were 77% and 43%, respectively, and were significantly higher in the low-dose group (P=0.02). Secondary: Clinical response rates in blastomycosis patients adherent to low- and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg PO QD ≥6 months			improved= undefined clinical and mycological response and non-compliant with protocol) Secondary: Response in patients treated for 6 months or more	high-dose ketoconazole therapy for ≥6 months were 79% and 100%, respectively (P=0.01). Response rates in histoplasmosis patients adherent to low- and high-dose ketoconazole therapy for ≥6 months were 92% and 71%, respectively (P=0.16).
Candidiasis (Esophageal/Oropharyngeal)				
Akova et al.[53] (1994) Fluconazole 200 mg daily IV during neutropenia, then 100 mg orally daily for 14 days (oropharyngeal involvement) or 21 days (esophageal involvement)	OL, PRO Adult patients with a hematological malignancy or solid tumor with oropharyngeal and/or esophageal candidiasis	N=129 4 week posttreatment follow-up	Primary: Clinical response	Primary: The overall clinical cure rate was 82%. Cure rates were similar in patients with and without esophageal involvement (75% and 83%, respectively, P>0.1). The overall mycological eradication rate was 56%.
Pagani et al.[54] (2002) Fluconazole 150 mg weekly (secondary prophylaxis) vs placebo	DB, PC, PRO, RCT Patients ≥16 years of age with HIV and oropharyngeal candidiasis who had responded to a 7 day course of fluconazole 200 mg daily	N=138 37 months	Primary: Third relapse of oropharyngeal candidiasis, occurrence of adverse events requiring discontinuation of the drug, development of microbiological resistance to fluconazole	Primary: The duration of secondary prophylaxis for patients receiving fluconazole and placebo were 347 and 197 days, respectively (P<0.001). The median time interval to relapse for patients receiving fluconazole and placebo were: first relapse (175 and 35 days, P<0.001), second relapse (68 and 43 days, P=0.027), and third relapse (41 and 41 days), respectively. Significantly more patients in the placebo group experienced a third relapse by day 196 compared to the number of patients in the fluconazole group suffering a third relapse by day 382 (50% and 25%, respectively, P<0.001). Relapse rates were 61% and 90% for patients receiving fluconazole and placebo, respectively (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No adverse events led to drug discontinuation. The difference in microbiological resistance between patients receiving fluconazole and those receiving placebo was not statistically significant (P=0.20).
Wilcox et al.[55] (1997) Fluconazole 100 mg to 200 mg orally daily for 3 to 8 weeks vs itraconazole 100 mg to 200 mg orally daily for 3 to 8 weeks	DB, MC, RCT Patients ≥13 years of age with endoscopically confirmed esophageal candidiasis and predisposing risk factors for fungal infection	N=126 4 week posttreatment follow-up	Primary: Clinical response Secondary: Severity of symptoms, mycological assessment (eradication), fungal culture, global efficacy at 4 week follow-up (Persistent response or relapse), time to clinical response, time to relapse	Primary: Clinical response rates (cured or improved) in patients receiving itraconazole and fluconazole were 94% and 91%, respectively. The difference was not statistically significant. Secondary: Clearance of all symptoms in patients receiving itraconazole and fluconazole occurred in 94% and 93%, respectively. Of those receiving itraconazole and fluconazole, 78% and 74%, respectively, remained symptom-free at the end of follow-up. The endoscopic assessment classified 94% of patients in both groups as cured or improved, respectively. Mycological eradication in patients receiving itraconazole and fluconazole occurred in 92% and 78%, respectively. Neither endoscopic nor mycological assessment demonstrated a statistically significant difference between treatment groups. Relapse rate at end of 4 weeks for patients receiving itraconazole and fluconazole was 18% and 27%, respectively. There was no significant difference between groups in time to relapse or response.
De Wit et al.[56] (1998) Fluconazole 150 mg orally for 1 dose	CS, OL, RCT Patients 16-65 years of age with HIV infection and oropharyngeal	N=40 30-day posttreatment follow-up	Primary: Clinical response and mycological eradication	Primary: At the end of treatment, clinical cure was observed in 75% of fluconazole patients and 24% of itraconazole patients. Improvement was observed in 15% and 12% of patients, respectively. Cure plus improvement was seen in significantly more fluconazole patients compared to itraconazole patients (P=0.0006).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs itraconazole 100 mg daily for 7 days	candidiasis			On the day of relapse or day 30, clinical success (cure plus improvement) was significantly higher in the fluconazole group compared to the itraconazole group (42% and 12% respectively, P=0.0013). Eradication was observed in 1 patient in each group.
Oude Lashof et al.[57] (2004) Fluconazole 100 mg daily for 10 days vs itraconazole 200 mg daily for 15 days	MC, OL, RCT Patients 16 years of age and older with cancer and oropharyngeal candidiasis	N=252 42 days	Primary: Clinical response (cure=resolution of signs and symptoms) and mycological response	Primary: Clinical cure was observed in 74% of fluconazole patients and 62% of itraconazole patients (P=0.04). Mycological eradication was observed in 80% of fluconazole patients and 68% of itraconazole patients (P=0.03). Both clinical cure and mycological eradication was observed in 66% of fluconazole patients and 54% of itraconazole patients (P=0.054).
Phillips et al.[58] (1998) Fluconazole 100 mg daily for 14 days vs itraconazole 100 mg daily for 14 days (itraconazole QD) vs itraconazole 100 mg twice daily for	DB, MC, PC, RCT HIV-infected patients ≥18 years of age with pseudomembranous oropharyngeal candidiasis	N=194 2 week posttreatment follow-up	Primary: Clinical response (complete= clearance of signs and symptoms except erythema, or markedly improved based on investigator ratings) and mycological response	Primary: Clinical response (complete or marked improvement) in patients receiving fluconazole, itraconazole QD and itraconazole BID was 90%, 90% and 82%, respectively. There was no significant difference in efficacy between the treatment groups. At day 7, cultures were negative in 56% of patients in the itraconazole BID group, 58% in the itraconazole QD group, and 44% in the fluconazole group. At day 14, cultures were negative in 44% of patients in the itraconazole BID group, 57% in the itraconazole QD group, and 53% in the fluconazole group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
7 days (itraconazole BID)				
Graybill et al.[59] (1998) Fluconazole 100 mg daily for 14 days vs itraconazole 200 mg daily for 7 days vs itraconazole 200 mg daily for 14 days	MC, OL, RCT Patients ≥13 years of age with HIV and oropharyngeal candidiasis	N=179 6 weeks	Primary: Clinical response (cured=clearance of all signs and symptoms; improved= minimal signs and symptoms with no visible lesions) Secondary: Symptom severity, quantification of colony-forming units (CFUs) of *Candida* (cure ≤20 colony forming units/mL), culture results	Primary: Cure was achieved in 97%, 86% and 87% of patients receiving itraconazole for 14 days, itraconazole for 7 days and fluconazole, respectively. Differences in clinical response were not statistically significant. Secondary: No significant differences were observed between groups in any secondary endpoint. Mycological cure was 52%, 88%, and 77% in patients receiving itraconazole for 14 days, itraconazole for 7 days and fluconazole, respectively.
Meunier et al.[60] (1990) Fluconazole 100 mg daily vs ketoconazole 400 mg daily	CS, DB, RCT Patients with cancer and mycologically proven oropharyngeal candidiasis	N=40 4-27 days	Primary: Clinical response and mycological response	Primary: Clinical cure was observed in 15 of 19 patients in the fluconazole group and 14 of 18 patients in the ketoconazole group. Mycological eradication was reported in 10 patients in both groups.
Hernandez-Sampelayo et al.[61] (1994) Fluconazole suspension	MC, OL, RCT Pediatric patients with AIDS or HIV infection and oropharyngeal	N=46 4 week posttreatment follow-up	Primary: Clinical response (cure=resolution of signs and symptoms), mycological	Primary: Clinical cure at the end of therapy was observed in 87.5% of fluconazole patients and 81% of ketoconazole patients. At the 4 week posttreatment follow-up, 44.4% of fluconazole and 58.8% of ketoconazole patients were clinically cured.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
3 mg/kg/day (for 5-49 days) vs ketoconazole suspension 7 mg/kg/day (for 5-49 days)	candidiasis		response (cure= negative culture)	At the end of therapy, mycological cure was observed in 71.4% of fluconazole patients and 57.1% of ketoconazole patients. At the 4 week posttreatment follow-up, 41.2% of fluconazole and 50.0% of ketoconazole patients were mycologically cured.
Vazquez et al.[62] (2006) Fluconazole 200 mg on day 1, then 100 mg daily for 13 days vs posaconazole 200 mg on day 1, then 100 mg daily for 13 days	MC, RCT, SB Patients ≥18 years of age with HIV and pseudomembranous oropharyngeal candidiasis	N=350 42 days	Primary: Clinical success (cure=absence of plaques and no or minimal symptoms, or improvement= partial resolution) on day 14 Secondary: Clinical durability or relapse on day 42, clinical response after 7 days of therapy, mycological response rate by visit (success= culture yielding <20 CFU/mL of *Candida* species, eradication= negative culture)	Primary: Clinical success rates observed in patients receiving posaconazole and fluconazole at day 14 were 91.7% and 92.5%, respectively. The difference was not statistically significant. Secondary: Clinical relapse rates at day 42 in patients receiving posaconazole and fluconazole were 31.5% and 38.2%, respectively (P=0.24). Response rates in patients receiving posaconazole and fluconazole at day 7 were 97.0% and 96.9%, respectively. On day 14, 68% of patients in both groups achieved mycological response. At day 42, significantly more patients in the posaconazole group continued to have mycological response compared to the fluconazole group (40.6% and 26.4%, P=0.038). Mycological eradication was observed in 35.6% of posaconazole patients and 24.2% of fluconazole patients at day 42 (P=0.084).
Ally et al.[63] (2001) Fluconazole 400	DB, MC, PC, RCT Immuno-compromised	N=391 43 days	Primary: Endoscopic response to treatment (cure=	Primary: The incidence of endoscopically proven cure in patients receiving voriconazole and fluconazole was 94.8% and 90.1%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg orally daily on day 1, then 200 mg daily vs voriconazole 200 mg orally twice daily	patients 18-75 years of age with esophageal and/or oropharyngeal candidiasis		normal endoscopy, improved= improvement in lesions of 1 or more grades) Secondary: Symptomatic response of esophageal and oropharyngeal candidiasis, time to symptomatic cure	Combined cured or improved response rates in patients receiving voriconazole and fluconazole were 98.3% and 95.1%, respectively. Secondary: Symptomatic cure was observed in 82.0% and 83.2% of voriconazole and fluconazole patients, respectively. The success rates for esophageal candidiasis were 88.0% and 91.1% in the voriconazole and fluconazole groups, respectively. The success rates for oropharyngeal candidiasis were 88.4% and 93.8% in the voriconazole and fluconazole groups, respectively. There was no significant difference in time to symptomatic cure.
Krause et al.[64] (2004) Fluconazole 200 mg oral loading dose on day 1, then 100 mg daily for 14-21 days vs anidulafungin 100 mg loading dose on day 1, then 50 mg IV daily	DB, MC, RCT Patients 18-65 years of age with esophageal candidiasis and a predisposing risk factor for fungal infection	N=601 Up to 35 weeks	Primary: Endoscopic response at the end of therapy (cure= complete resolution of lesions; improvement= decrease of >1 grade from baseline) Secondary: Clinical response (absence or improvement in symptoms), mycological response (eradication)	Primary: Endoscopic success was observed in 97.2% of patients in the anidulafungin group and 98.8% of patients in the fluconazole group. No significant difference was observed. Secondary: Clinical success was observed in 97.2% of patients in the anidulafungin group and in 98% in the fluconazole group. No significant difference was observed. Mycological success was observed in 86.7% of patients in the anidulafungin group and in 90.9% in the fluconazole group.
Villanueva et al.[65] (2002) Fluconazole 200	DB, MC, RCT Patients with symptomatic,	N=177 5-7 day posttreatment	Primary: Combined clinical and endoscopic response	Primary: Combined response rates in patients receiving caspofungin and fluconazole were 81% and 85%, respectively. No significant difference was seen between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg IV daily for 7 to 21 days vs caspofungin 50 mg IV daily for 7 to 21 days	endoscopically and microbiologically documented *Candida* esophagitis	follow-up	(favorable= complete resolution of signs and symptoms and total clearing of esophageal lesions or reduction in endoscopy score by at least 2 points), microbiological response (negative stains and culture)	Microbiological response was observed in 59% of patients in the caspofungin group and 76% of patients in the fluconazole group.
de Wet et al.[66] (2004) Fluconazole 200 mg IV daily for up to 14-21 days vs micafungin 50 mg, 100 mg, or 150 mg IV daily for up to 14-21 days	DB, MC, PG, RCT Patients 18 years of age or older with HIV infection and endoscopically confirmed esophageal candidiasis (EC)	N=245 2 week posttreatment follow-up	Primary: Endoscopic cure rate and eradication rates Secondary: Change in endoscopic cure rate compared with baseline at day 14, clinical response at end of treatment, EC severity score, overall therapeutic success, incidence of relapse	Primary: Comparisons of micafungin groups showed a dose-response relationship for endoscopic cure. Cure rates were 68.8%, 77.4%, and 89.9% for the 50-mg, 100-mg, and 150-mg doses, respectively (P=0.024 for comparison between the 3 groups, P=0.007 for the comparison of the 50-mg and 150-mg groups). There was no significant difference seen between the fluconazole group and either the 100-mg or 150-mg micafungin groups (P=0.136 and P=0.606, respectively). Fluconazole had a lower endoscopic cure rate than micafungin 150 mg in patients with an endoscopic grade 3 at baseline (77.8% and 100% respectively). Eradication rates were 35.1%, 78.3%, 57.1%, and 67.3% for the micafungin 50-mg, 100-mg, and 150-mg groups and the fluconazole group, respectively. Eradication rates for the micafungin 100-mg group were higher than for the 150-mg group (P=0.031). No significant difference was observed between micafungin 100 mg and fluconazole or micafungin 150 mg and fluconazole (P=0.263 and P=0.312, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: All treatment groups showed an improvement in endoscopic findings at the end of treatment compared to baseline (P=0.003 for the micafungin groups). Endoscopic cure rate at day 14 and clinical response at the end of treatment were dose dependent in the micafungin groups and comparable in the 100-mg and 150-mg micafungin group and the fluconazole group (P=0.574). Therapeutic success rates were comparable among the 100-mg and 150-mg micafungin groups and the fluconazole group (P=0.463). The rates of improvement in EC severity scores were comparable in the 100-mg and 150-mg micafungin groups and the fluconazole group. Worsening EC severity or use of non-prophylactic antifungal therapy was observed in 9 patients in the micafungin group during follow-up and in no patients in the fluconazole group.
de Wet et al.[67] (2005) Fluconazole 200 mg IV for up to 42 days vs micafungin 150 mg IV daily for up to 42 days	DB, MC, PG, RCT Patients 16 years of age and older with endoscopically confirmed esophageal candidiasis (EC)	N=523 4 week posttreatment follow-up	Primary: Treatment success at the end of therapy (endoscopic cure, mucosal grade=0) Secondary: Clinical and mucosal response at the end of therapy (cleared or improved), therapeutic response at the end of therapy, relapse at 2 and 4 weeks posttreatment	Primary: Endoscopic cure rate was 87.7% at the end of therapy in the micafungin group compared to 88.0% for fluconazole patients and no significant differences were observed. Secondary: The clinical success rates (cleared or improved) for micafungin and fluconazole were 94.2% and 94.6% respectively. Overall therapeutic success rates for micafungin and fluconazole were 87.3% and 87.2%, respectively. The overall incidence of relapse at 2 and 4 weeks posttreatment was 15.2%and 11.3% in the micafungin and fluconazole groups, respectively (P>0.313).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Blomgren et al.[68] (1998) Fluconazole 50 mg orally daily for 7 days vs nystatin rinse with 1 mL for 5 minutes 4 times daily for 3 weeks	RCT Patients with a diagnosis of oral candidiasis	N=71 6 month posttreatment follow-up	Primary: Clinical response (cure=healthy oral mucosa and no signs and symptoms)	Primary: No significant differences were observed between groups in clinical response.
Flynn et al.[69] (1995) Fluconazole 4 mg/kg oral loading dose, followed by 2 mg/kg daily for 14 days vs nystatin 400,000 units 4 times daily for 14 days The dose of fluconazole was increased half-way through the study to 6 mg/kg loading dose followed by 3 mg/kg daily.	MC, RCT, SB Children 5 months to 14 years of age with oral thrush	N=182 42 days	Primary: Clinical response (cure=resolution of symptoms and signs of infection; improvement= reduction in signs and symptoms), mycological response (negative culture)	Primary: Significantly more patients treated with fluconazole were clinically cured (78% and 37%, respectively, P<0.001). Significantly more patients treated with fluconazole experienced mycological eradication (55% and 6%, respectively, P<0.001). At the end of therapy, significantly more patients taking the higher dose of fluconazole had mycological eradication compared to the lower dose (P<0.01).
Goins et al.[70] (2002)	OL, PRO, RCT	N=34	Primary: Clinical response	Primary: At the end of therapy, 28.6% of nystatin patients and 100% of fluconazole

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluconazole 3 mg/kg/day orally for 7 days vs nystatin 100,000 units 4 times daily for 10 days	Infants 1-12 months of age with signs of oral thrush	28 days	(cure=absence of oral plaques), microbiologic response (cure= negative culture)	patients were clinically cured (P<0.0001). At the end of therapy, 5.6% of nystatin patients and 73.3% of fluconazole patients were microbiologically cured (P<0.0001). By day 28, 23% of fluconazole patients had evidence of clinical relapse (relapse not evaluated in nystatin group).
Pons et al.[71] (1997) Fluconazole 200 mg oral loading dose, followed by 100 mg orally once daily for 14 days vs nystatin 500,000 units four times daily for 14 days	MC, PRO, RCT Patients with AIDS or HIV and typical signs and symptoms of oropharyngeal candidiasis	N=167 42 days	Primary: Clinical response (cure=complete resolution of signs and symptoms), mycological response (cure= eradication)	Primary: Significantly more patients in the fluconazole group were considered clinically cured compared to patients in the nystatin group (87% and 52% respectively, P<0.001). Significantly more patients in the fluconazole group experienced mycological eradication compared to the nystatin group (60% and 6% respectively, P<0.001).
Saag et al.[72] (1999) Itraconazole 100 mg orally twice daily for 14 days Patients not responding completely were treated with an additional 14 days of itraconazole	MC, OL Patients 18-65 years of age with HIV and oropharyngeal candidiasis who had failed ≥14 days treatment of fluconazole ≥200 mg daily within past 14 days	N=74 6 week posttreatment follow-up	Primary: Clinical response at end of treatment (no lesions or symptoms)	Primary: Clinical response was observed in 55% of patients. All patients who did not receive maintenance itraconazole therapy after initial therapy relapsed within 6 weeks.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
solution.				
Queiros-Telles et al.[73] (2001) Itraconazole 100 mg orally twice daily for 7-14 days	MC, OL Patients >18 years of age with HIV and pseudomembranous oropharyngeal candidiasis	N=50 4 weeks	Primary: Clinical response at end of therapy (success=cured or improved, undefined), mycological cure (negative culture)	Primary: Clinical response was observed in 86% and 92% of patients after 7 and 14 days, respectively, and maintained for 21 days following therapy in 52% of patients. Mycological cure was observed in 40% of patients at the end of therapy but *Candida* colonization occurred in 84% of patients at day 28.
Smith et al.[74] (1991) Itraconazole 200 mg daily for 28 days vs ketoconazole 200 mg twice daily for 28 days	DB, RCT Patients with HIV infection and clinical and mycological diagnoses of buccal or esophageal candidiasis	N=111 3 month posttreatment follow-up	Primary: Clinical response (resolution of signs or improvement in signs by 2 or more grades), mycological response (negative culture)	Primary: There was no significant difference between groups in clinical response rates (P>0.4497). There was no significant difference between groups in mycological response rates by week 4. At week 1, the mycological response rate was greater in the ketoconazole group compared to the itraconazole group (P=0.0028), but this difference did not persist.
de Repentigny et al.[75] (1996) Itraconazole 200 mg daily vs ketoconazole 200 mg daily Patients were treated for 2 weeks (oropharyngeal candidiasis) or 4	DB, MC, PC, RCT Patients 16 years of age and older with symptoms and signs of oropharyngeal and/or esophageal candidiasis and HIV	N=143 6 week posttreatment follow-up	Primary: Clinical response (cure=no signs and symptoms of disease), mycological response for oropharyngeal patients only (cure=negative culture)	Primary: There was no significant difference in clinical cure rates with itraconazole compared to ketoconazole for patients with oropharyngeal or esophageal candidiasis (P=0.0614 and *P*=0.0781, respectively). Mycological cure occurred in 63% of itraconazole patients and 62% of ketoconazole patients with oropharyngeal candidiasis (P=0.8589).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks (esophageal candidiasis).				
Murray et al.[76] (1997) Itraconazole 200 mg orally daily for 14 days vs clotrimazole troches 10 mg five times daily for 14 days	MC, OL Patients ≥13 years of age with oropharyngeal candidiasis and predisposing risk factors for immunosuppression	N=149 6 weeks	Primary: Clinical response (cured=clearance of all symptoms; improved= minimal symptoms and no lesions), mycological response (negative culture)	Primary: Clinical (77% and 70%, P=0.349), mycological (60% and 32%, P<0.001), and clinical and mycological (53% and 30%, P=0.006) responses were observed in patients receiving itraconazole and clotrimazole, respectively. Mycological (64% and 29%) and clinical plus mycological (55% and 28%) were observed in the subset of HIV/AIDS patients receiving itraconazole and clotrimazole, respectively (P<0.01).
Linpiyawan et al.[77] (2000) Itraconazole 100 mg orally twice daily for 7 days vs clotrimazole troches 10 mg five times daily for 7 days	PRO, RCT Patients 15-62 years of age with AIDS and oropharyngeal candidiasis	N=29 4 weeks	Primary: Global evaluation of response, mycological response	Primary: Clinical cure rates in patients receiving itraconazole and clotrimazole were 66.7% and 73.3%, respectively. Differences in reduction in clinical severity scores and clinical plus mycological response were not statistically significant between the treatment groups.
Petersen et al.[91] (1980) Ketoconazole 100 mg (<40 kg) or 200 mg (≥40 kg) orally daily vs	DB, PC, RCT Patients 7-31 years of age with chronic mucocutaneous candidiasis for ≥3 years	N=12 6 months	Primary: Clinical response	Primary: Symptom remission and regression of mucosal, nail and skin lesions of patients receiving ketoconazole and placebo occurred in 100% and 0%, respectively. Temporary mucosal clearing occurred in 33.3% of patients receiving placebo. The response was significantly more favorable in patients receiving ketoconazole than placebo (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Skiest et al.[78] (2007) Posaconazole 400 mg orally twice daily for 3 days, then 400 mg daily for 25 days (regimen A) vs posaconazole 400 mg orally twice daily for 28 days (regimen B) Patients responding to initial treatment received 400 mg twice daily 3 times per week as maintenance therapy,	MC, OL Patients ≥18 years of age with HIV and oropharyngeal or esophageal candidiasis who had failed fluconazole or itraconazole treatment for mucosal candidiasis	N=176 4 week posttreatment follow-up	Primary: Rate of cure or improvement after 28 days of therapy Secondary: Clinical response on day 14, clinical response at day 14 stratified by the presence or absence of in vitro resistance to fluconazole or itraconazole at baseline	Primary: Clinical response rates at 28 days in patients receiving regimen A and regimen B were 75.3% and 74.7%, respectively. Secondary: At day 14, 52.8% of patients were considered responders. Clinical response in all patients with baseline fluconazole resistance, itraconazole resistance, or resistance to both agents was 73%, 74% and 74%, respectively. Relapse rates were 80% and 68% of all patients receiving posaconazole QD and BID, respectively.
Candidiasis (Systemic)				
Phillips et al.[35] (1997) Fluconazole 800 mg IV loading dose on day 1, then 400 mg IV daily for 4 week	RCT, SB Patients ≥18 years of age with one or more blood cultures positive for a yeast species	N=106 6 months	Primary: Clinical response (success=absence of death within the first 7 days of treatment, progressive fungal infection, and withdrawal from	Primary: Successful response was seen in 50% of fluconazole patients and 58% of amphotericin B patients (P=0.39). Therapy failed in 1 amphotericin B patient during the sixth months of follow-up.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amphotericin B 0.6 mg/kg/day IV Patients could be switched to oral fluconazole after 10 days of IV therapy if fungemia had cleared and they could tolerate oral therapy.			study due to drug toxicity, inadequate response, or superinfection)	
Abele-Horn et al.[36] (1996) Fluconazole 400 mg on day 1, then 200 mg daily IV for 14 days vs amphotericin B 1-1.5 mg/kg/day every other day for 14 days plus flucytosine 3×2.5 g as a total daily dose	MC, PRO, RCT Patients 18-80 years of age in the intensive care unit (ICU) with evidence of systemic *Candida* infection	N=72 14 days	Primary: Clinical response (cure=resolution of all symptoms and signs of infection), microbiological response (cure= eradication of *Candida* species)	Primary: No significant differences were seen between the treatment groups in the treatment of pneumonia and sepsis/fungemia. In the treatment of peritonitis, amphotericin B plus flucytosine was more effective than fluconazole, as seen in clinical and microbiological response (P<0.05).
Kujath et al.[37] (1993) Fluconazole 400 mg on day 1, then 300 mg IV daily	OL, PRO, RCT Patients ≥18 years of age with systemic candidiasis	N=40 Variable duration	Primary: Microbiological response (elimination or improvement [reduction of	Primary: No statistical difference was observed between groups in microbiological elimination or improvement (P=0.44). Fungal elimination was observed significantly sooner in the amphotericin B plus flucytosine group compared to the fluconazole group (5.5 days and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amphotericin B 0.5 mg/kg/day IV plus flucytosine 3×2.5 g as a total daily dose			fungal density by 2 stages on a 6-stage scale]), time to elimination of all fungi	8.5 days respectively, P=0.03).
Rex et al.[38] (1994) Fluconazole 400 mg daily IV for 7 days, followed by oral therapy vs amphotericin B 0.5-0.6 mg/kg/day IV for the first 7 days, then 3 times per week	MC, RCT Patients 13 years of age and older with at least 1 positive blood culture for *Candida* species	N=237 12 week posttreatment follow-up	Primary: Response rates (success= resolution of signs and symptoms and negative blood cultures) Secondary: Response rates in the intent-to-treat population, outcome in patients who received at least 5 days of therapy	Primary: No significant difference was observed between fluconazole and amphotericin B in successful response to therapy (70% and 79% respectively, P=0.22). Secondary: No significant difference was observed in the intent-to-treat population between fluconazole and amphotericin B in successful response to therapy (72% and 80% respectively, P=0.17). In patients who had received at least 5 days of treatment, 75% of fluconazole patients and 86% of amphotericin B patients had a successful outcome (P=0.05).
Reboli et al.[39] (2007) Fluconazole 800 mg IV on day 1 then 400 mg daily for 14-42 days vs anidulafungin 200 mg IV on day 1, then 100 mg daily	DB, MC, RCT Patients 16 years of age and older with candidemia or other forms of invasive candidiasis	N=261 6 week posttreatment follow-up	Primary: Global response at the end of IV therapy (success= resolution of signs and symptoms and no need for additional antifungal therapy and eradication of *Candida* species) Secondary:	Primary: Significantly more patients in the anidulafungin group achieved a successful global response compared to the fluconazole group (75.6% and 60.2% respectively, P=0.01). Secondary: Significantly more patients in the anidulafungin group had a successful global response at the end of all therapy compared to the fluconazole group (74% and 56.8% respectively, P<0.02). Significantly more patients in the anidulafungin group had a successful global response at the 2-week follow-up compared to the fluconazole group (64.6% and 49.2% respectively, P<0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 14-42 days All patients could receive oral fluconazole after 10 days of IV therapy if they could tolerate oral medication, if they were afebrile for 24 hours, last blood culture was negative for *Candida*, and if there was clinical improvement.			Global response at the end of all therapy and at 2 and 6 weeks follow-up, per-patient and per-pathogen microbiological response at all time points, death from all causes	There was no significant difference in the proportion of patients in either group who had a successful global response at the 6-week follow-up (55.9% and 44.1% respectively). Microbiological success was observed for 88.1% of all pathogens in the anidulafungin group compared to 76.2% in the fluconazole group (P=0.02). There was no significant difference in death from all causes between groups (P=0.13).
Reboli et al.[125] (2011) Fluconazole 800 mg IV on day 1 then 400 mg daily for 14-42 days vs anidulafungin 200 mg IV on day 1, then 100 mg daily for 14-42 days All patients could receive oral fluconazole after 10 days of IV therapy if they could tolerate oral	DB, MC, RCT (Post-hoc analysis) Patients 16 years of age and older with candidemia or other forms of invasive candidiasis	N=261 6 week posttreatment follow-up	Primary: Baseline characteristics predictive of treatment success	Primary: There were no significant imbalances in any baseline clinical or demographic characteristics between the two treatment groups (P≤ 0.05). Study treatment and APACHE II score were identified as significant and independent predictors of global response at the end of the IV study treatment in patients with invasive *C. albicans* infection. The odds ratio for study treatment was 2.60 (95% CI, 1.14-5.91) in favor of anidulafungin, and the odds ratio for APACHE II score was 0.935 (95% CI, 0.885-0.987), with poorer responses associated with higher baseline APACHE II scores. The proportion of patients who died during the 6-week period from study entry was 20.3% in the anidulafungin arm and 21.3% in the fluconazole arm. The Kaplan-Meier estimates of survival at 6 weeks were not significantly different between treatment groups (P=0.842).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
medication, if they were afebrile for 24 hours, last blood culture was negative for *Candida*, and if there was clinical improvement.				
Kulberg et al.[40] (2005) Voriconazole 6 mg/kg IV every 12 hours for 1 day, then 3 mg/kg every 12 hours vs amphotericin B 0.7-1.0 mg/kg/day Patients in the voriconazole could be switched to oral voriconazole 200 mg twice daily after 3 days, and patients in the amphotericin group were switched to IV or oral fluconazole after 3-7 days.	MC, RCT Patients 12 years of age and older with candidemia	N=370 12 week posttreatment follow-up	Primary: Response to treatment (clinical cure or improvement and microbiological eradication) Secondary: Time to first negative blood culture, time from randomization to death	Primary: No significant difference between groups was observed in successful response to treatment (P=0.96). Significantly more patients in the voriconazole group infected with *C. tropicalis* were considered to have a successful response compared to the amphotericin group (32% and 6% respectively, P=0.032). Secondary: No significant difference between groups was observed in the time to first negative blood culture (2 days in each group). No significant difference between groups was observed in the time from randomization to death (36% in the voriconazole group died in the first 14 days compared to 42% in the amphotericin B group).
Gafter-Gvili et al.[119] (2008)	MA Patients with	N=3,265 (15 trials)	Primary: 30-day all-cause mortality	Primary: <u>Fluconazole vs other antifungal agents (9 studies)</u> No difference in mortality was observed with fluconazole vs amphotericin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<u>Group 1</u> Echinocandins vs other antifungal agents <u>Group 2</u> Fluconazole vs other antifungal agents	confirmed invasive candidiasis	Variable duration	Secondary: Treatment failure, microbiological failure, adverse events	B (RR, 0.92; 95% CI, 0.72-1.17). No difference in mortality was observed between fluconazole and itraconazole (RR, 1.91; 95% CI, 0.39-9.35) or between fluconazole and a combination of fluconazole and amphotericin B (RR, 0.98; 95% CI, 0.70-1.35). <u>Echinocandins vs other antifungal agents (4 studies)</u> There was no difference in mortality with anidulafungin vs fluconazole (RR, 0.73; 95% CI, 0.48-1.10). There was no difference in mortality with caspofungin vs amphotericin B (RR, 1.08; 95% CI, 0.75-1.55) or with micafungin vs liposomal amphotericin B (RR, 1.04; 95% CI, 0.75-1.43). <u>Other comparisons (2 studies)</u> There was no difference in mortality with micafungin vs caspofungin (100 mg/d: RR, 1.10; 95% CI, 0.80-1.51; 150 mg/d: RR, 1.27; 95% CI, 0.93-1.72). There was no difference in mortality with amphotericin B plus fluconazole vs voriconazole (RR, 1.18; 95% CI, 0.90-1.54). Secondary: <u>Fluconazole vs other antifungal agents (9 studies)</u> No significant difference in treatment failure was found with fluconazole and amphotericin B (RR 1.22; 95% CI, 0.97-1.54) or with fluconazole vs a combination of fluconazole and amphotericin B (RR 1.41; 95% CI, 0.99-1.99). Microbiological failure was higher in patients treated with fluconazole compared to amphotericin B (RR 1.52; 95% CI, 1.12-2.07) or with fluconazole vs a combination of fluconazole and amphotericin B (RR 2.69; 95% CI, 1.17-6.18). No difference in adverse events requiring discontinuation was noted with fluconazole vs amphotericin B (RR 0.45; 95% CI, 0.13-1.56), itraconazole

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(RR 0.32; 95% CI, 0.04-2.82) or with fluconazole vs a combination of fluconazole and amphotericin B (RR 1.16; 95% CI, 0.49-2.75). Fluconazole caused less nephrotoxicity than amphotericin B (RR, 0.11; 95% CI, 0.03-0.48) or the combination of amphotericin B and fluconazole (RR, 0.12; 95% CI, 0.04-0.39). <u>Echinocandins vs other antifungal agents (4 studies)</u> Treatment failure significantly decreased with anidulafungin vs fluconazole (RR, 0.61; 95% CI, 0.42-0.89). There was no difference in treatment failure with caspofungin vs amphotericin B (RR, 0.70; 95% CI, 0.47-1.03) or with micafungin vs liposomal amphotericin B (RR, 0.93; 95% CI, 0.74-1.19). Microbiological failure was significantly reduced with anidulafungin vs fluconazole (RR, 0.50; 95% CI, 0.29-0.86). No difference in microbiological failure was noted for caspofungin vs amphotericin B (RR, 0.95; 95% CI, 0.40-2.25) or with micafungin vs liposomal amphotericin B (RR, 1.01; 95% CI, 0.53-1.92). A significant decrease in adverse events requiring discontinuation was observed with anidulafungin vs fluconazole (RR, 0.52; 95% CI, 0.29-0.92). Caspofungin was associated with a significantly lower rate of adverse events requiring discontinuation when compared with amphotericin B (RR, 0.11; 95% CI, 0.04-0.36) or liposomal amphotericin B (RR, 0.45; 95% CI, 0.26-0.80). <u>Other comparisons (2 studies)</u> There was no difference in treatment failure with micafungin and caspofungin (100 mg/d: RR, 0.85; 95% CI, 0.60-1.20; 150 mg/d: RR, 1.04; 95% CI, 0.74-1.42). There was no difference in treatment failure with amphotericin B plus fluconazole vs voriconazole (RR, 1.00; 95% CI, 0.83-1.19). There was no difference in microbiological failure with micafungin and caspofungin (100 mg/d: RR, 0.73; 95% CI, 0.41-1.22; 150 mg/d: RR, 1.10; 95% CI, 0.70-1.73).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no difference in adverse events requiring discontinuation with micafungin and caspofungin. Adverse events requiring discontinuation were significantly lower (RR, 0.47; 95% CI, 0.23-0.93) and nephrotoxicity was significantly higher (RR, 2.64; 95% CI, 1.57-4.44) with the amphotericin B-fluconazole arm compared to voriconazole.
Candidiasis (Vaginal)				
Sobel et al.[112] (1995) Fluconazole 150 mg orally as a single dose vs clotrimazole tablet 100 mg intravaginally for 7 days	MC, PRO, RCT, SB Female patients 17-64 years of age with symptomatic *Candida* vaginitis	N=358 35 days	Primary: Clinical response at day 14 and 35 (cured=absence of signs and symp-toms of vaginitis; improved= reduction of >50% of the clinical severity score)	Primary: Clinical response at 14 days in patients receiving fluconazole and clotrimazole were 94% and 97%, respectively (P=0.307). At day 35, 75% of patients in both treatment groups were still clinically cured (P=0.890).
van Heusden et al.[113] (1994) Fluconazole 150 mg orally for one dose vs clotrimazole 500 mg intravaginally for one dose	CS, MC, RCT Patients 18-65 years of age with symptomatic vaginal candidosis	N=741 28 days	Primary: Clinical efficacy (symptom scores from 0=absent to 3=severe)	Primary: No significant difference was observed between groups in clinical efficacy (P=0.48). There was no significant difference observed between groups in mycological efficacy (tests not performed on all patients and not required by study protocol).
O-Prasertsawat et al.[114] (1995) Fluconazole 150	PRO, RCT, SB Patients with a clinical diagnosis of vulvovaginal	N=103 1- and 4-week posttreatment follow-up	Primary: Clinical improvement (Patient self-assessment based	Primary: At week 1, clinical improvement was reported in 87% of fluconazole patients and 90% of clotrimazole patients (P=0.92). At week 1, mycological cure was reported in 79.2% of fluconazole

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg orally for one dose vs clotrimazole 100 mg suppository intravaginally twice daily for 3 days	candidiasis		on symptoms, not further defined), mycological cure (negative culture)	patients and 80% of clotrimazole patients (P=0.88). At week 4, clinical improvement was reported in 69.8% of fluconazole patients and 68% of clotrimazole patients (P=0.99). At week 4, mycological cure was reported in 60.4% of fluconazole patients and 66% of clotrimazole patients (P=0.70).
Mendling et al.[115] (2004) Fluconazole 150 mg orally as single dose vs clotrimazole tablet 500 mg intravaginally as single dose plus clotrimazole 1% cream applied to vulval area as needed vs clotrimazole 10% cream intravaginally as single dose plus clotrimazole 2% cream applied to vulval area as	AC, MC, RCT, SB Female patients with vulvovaginal mycosis caused by *Candida*	N=679 8 weeks	Primary: Overall response (clinical cure and mycological response, undefined) at 14 days Secondary: Time to meaningful symptom relief and complete symptom relief	Primary: Overall response rates at 14 days in patients receiving clotrimazole tablet, clotrimazole cream and fluconazole were 65.8%, 60.5% and 59.1%, respectively. Secondary: The difference in time to meaningful or complete symptom relief was not statistically significant among groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
needed				
Sekhavat et al.[132] (2011) Fluconazole 150 mg as a single dose vs clotrimazole 200 mg daily intravaginally for 6 days	RCT Patients >15 years of age with acute clinical and mycologically verified vulvovaginal candidiasis	N=142 1 month	Primary: Clinical cure (defined as absence of signs and symptoms) and mycological cure (defined as microscopic absence of yeast)	Primary: On the first visit, *Candida* was clinically treated in 73.6% of patients in the fluconazole group and 58.6% of patients in the clotrimazole group. *Candida* was eradicated in 83.3% of patients in the fluconazole group and in 70% of patients in the clotrimazole group (P=0.001). After 1 month, *Candida* was recurrent symptomatically in 1 patient in the fluconazole group and 17 patients in clotrimazole group (P=0.001). Mycological symptoms were positive in 1 patient in the fluconazole group and 7 patients in clotrimazole group (P=0.01).
Pitsouni et al.[122] (2008) Fluconazole 150 mg orally for 1 dose vs itraconazole 200 mg twice daily for 1 day, itraconazole 200 mg once for 3 days, or itraconazole 200 mg twice daily for 7 days	MA Nonpregnant women with uncomplicated acute vaginal or vulvovaginal candidiasis	N=1092 (6 trials) 60 days	Primary: Clinical cure and mycologic cure at the first and second assessment visits after treatment was completed (7-28 days and 21-60 days, respectively) Secondary: Adverse events	Primary: There was no difference between itraconazole and fluconazole regarding clinical cure and improvement at the first and second scheduled visit assessments (OR 0.94; 95% CI, 0.6-1.48 and OR 1.09; 95% CI, 0.68-1.75, respectively). There was no difference between itraconazole and fluconazole regarding mycological cure at the first and second scheduled visit assessments (OR 0.73; 95% CI, 0.31-1.7 and OR 0.71; 95% CI, 0.49-1.03, respectively). Secondary: There was no difference between itraconazole and fluconazole regarding adverse events (OR 1.07; 95% CI, 0.42-2.73 and OR 1.84; 95% CI, 0.3-11.27, respectively). The proportion of patients with skin and subcutaneous tissues adverse events was 0% and 2% for fluconazole and 0% and 12% for itraconazole, respectively.
van Heusden et al.[116] (1990) Fluconazole 150	DB, MC, PG, RCT Patients 18-65 years of age with symptomatic and	N=99 3-12 day posttreatment follow-up	Primary: Clinical efficacy (cure, improve-ment, or failure assessed by	Primary: At the short-term follow-up, 100% of fluconazole patients and 94% of miconazole patients were considered cured or improved by investigators. At the long-term follow-up, 95% of fluconazole patients and 90% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg orally as a single dose vs miconazole 1,200 mg capsule intravaginally as a single dose	mycologically verified vaginal candidosis	(short-term follow-up), and 22-60 day posttreatment follow-up (long-term follow-up)	investigator, not further defined, combined with patient-rating of excellent, good, fair, or not effective), mycological efficacy (cure= negative culture)	miconazole patients were considered cured or improved by investigators. At the short-term follow-up, 81% of fluconazole patients and 84% of miconazole patients considered the treatment excellent or good. At the long-term follow-up, 81% of fluconazole patients and 76% of miconazole patients considered the treatment excellent or good. At the short-term follow-up, mycological cure was observed in 98% of fluconazole patients and 96% of miconazole patients. At the long-term follow-up, mycological cure was observed in 74% of fluconazole patients and 82% of miconazole patients.
Cryptococcal Disease				
Saag et al.[41] (1992) Fluconazole 400 mg oral loading dose, followed by 200 mg daily vs amphotericin B 0.3 mg/kg/day or an equivalent dose every other day Patients in the amphotericin B group may also have been treated with flucytosine 150 mg/kg/day according to investigator	MC, RCT Patients 18 years of age and older with HIV and a positive cerebrospinal fluid (CSF) culture for *Cryptococcus neoformans*	N=194 10 weeks	Primary: Rate of treatment success (sterilization of CSF cultures)	Primary: Treatment was successful in 40% of the amphotericin B patients and 34% of the fluconazole patients (P=0.40). Disease progression occurred more frequently in the fluconazole group while discontinuation of study drug occurred more frequently in the amphotericin B group though neither difference was statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
discretion.				
Larsen et al.[42] (1990) Fluconazole 400 mg orally for 10 weeks vs amphotericin B 0.7 mg/kg/day IV for 7 days, followed by 3 times weekly for 9 weeks plus flucytosine 150 mg/kg/day orally in 4 doses for 10 weeks	PRO, RCT Patients 18 years of age and older with evidence of cryptococcal meningitis, with or without acquired immunodeficiency syndrome (AIDS)	N=26 62 weeks	Primary: Clinical outcome (success=blood and cerebrospinal fluid cultures negative)	Primary: At 10 weeks of treatment, 8 of 14 patients receiving fluconazole were considered failures while 0 of 6 patients taking amphotericin B plus flucytosine were considered failures (P=0.04). Conversion from positive to negative CSF cultures was significantly slower in patients taking fluconazole compared to amphotericin B and flucytosine (P=0.02). No significant difference was seen in the time to achieve mycological success for blood cultures (P=0.19).
van der Horst et al.[43] (1997) <u>Step 1</u> Amphotericin B 0.7 mg/kg/day plus flucytosine 100 mg/kg/day in 4 doses for 2 weeks vs amphotericin B 0.7 mg/kg/day for 2 weeks Patients who were	DB, MC, RCT Patients ≥13 years of age with first episode of AIDS-associated cryptococcal meningitis	N=381 (Step 1) N=306 (Step 2) 10 weeks	Primary: Mycological response (negative culture) at 2 and 10 weeks, clinical outcome (success= resolution of fever, headache, and meningismus) at 2 and 10 weeks	Primary: Mycological response at the end of step 1 in patients receiving amphotericin B plus flucytosine or amphotericin B alone was 60% and 51%, respectively (P=0.06). Clinical response at the end of step 1 in patients receiving amphotericin B plus flucytosine or amphotericin B alone was 78% and 83%, respectively (P=0.18). There was no significant difference between the treatments in combined mycological and clinical response (P=0.12). Mycological response at the end of step 2 in patients receiving fluconazole and itraconazole was 72% and 60%, respectively. Clinical response at the end of step 2 in patients receiving fluconazole and itraconazole was 68% and 70%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
stabilized or improved after step 1 moved on to step 2. <u>Step 2</u> Fluconazole 800 mg daily for 2 days, followed by 400 mg daily for 8 weeks vs itraconazole 600 mg daily for 3 days, followed by 200 mg twice daily for 8 weeks				There was no significant difference between fluconazole and itraconazole in mycological or clinical response.
Brouwer et al.[44] (2004) Fluconazole 400 mg daily plus amphotericin B 0.7 mg/kg/day vs fluconazole 400 mg daily plus flucytosine 100 mg/kg/day plus amphotericin B 0.7 mg/kg/day vs	OL, RCT Adult patients with first episode of cryptococcal meningitis and HIV	N=64 10 weeks	Primary: Rate of reduction of CSF cryptococcal colony-forming units	Primary: Early fungicidal activity occurred faster for patients receiving amphotericin B plus flucytosine than amphotericin B alone (P=0.0006), amphotericin B plus fluconazole (P=0.03), or amphotericin B plus flucytosine plus fluconazole (P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amphotericin B 0.7 mg/kg/day plus flucytosine 100 mg/kg/day vs amphotericin B 0.7 mg/kg/day After 2 weeks, all arms received treatment with fluconazole 400 mg daily for 8 weeks, followed by 200 mg daily.				
Nussbaum et al.[127] (2010) Fluconazole 1,200 mg daily for 14 days vs fluconazole 1,200 mg daily plus flucytosine 100 mg/kg/day, followed by fluconazole 800 mg/day	OL, RCT HIV-positive adults with their first episode of cryptococcal meningitis	N=41 24 days	Primary: Rate of CSF infection clearance	Primary: The rate of clearance of infection was more rapid in the combination arm compared with fluconazole alone. The difference in EFA was 0.18 (95% CI, 0.085 to 0.27; P=0.0005). Four patients in the combination arm and 1 in the monotherapy arm had sterile CSF cultures by day 14.
Dermatophyte Infections				
Dehghan et al.[137] (2010)	RCT, DB	N=105	Primary: Clinical response	Primary: After 2 weeks, the rate of complete resolution of disease was significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluconazole 400 mg as a single dose (G1) vs clotrimazole 1% cream twice daily for 2 weeks (G2)	Patients with pityriasis versicolor	12 weeks	and recurrence rates	higher in the clotrimazole group than in the fluconazole group (49.1% vs 30%, respectively' P=0.16). After 4 weeks, 81.2% of patients in the fluconazole group and 94.9% of patients in the clotrimazole group showed complete resolution (P=0.044). After 12 weeks, 92% of patients in the fluconazole group and 81.8% of patients in the clotrimazole group showed complete resolution. Recurrence rate in the fluconazole and clotrimazole groups were 6% and 18.2%, respectively (P=0.77). No complications were seen in either group.
Roberts et al.[45] (1987) Ketoconazole 200 mg daily for up to 8 weeks vs griseofulvin 1 g daily for up to 8 weeks	RCT Patients with mycologically proven tinea pedis	N=29 8 weeks	Primary: Mycological cure (negative culture)	Primary: At 4 weeks, the mycological cure rate was 33% in the ketoconazole group and 29% in the griseofulvin group. At 8 weeks, the mycological cure rate was 53% in the ketoconazole group and 57% in the griseofulvin group.
Jolly et al.[46] (1983) Ketoconazole 200 mg daily for 2-16 weeks vs griseofulvin ultramicrosize 250 mg daily for 2-16 weeks	DB, RCT Patients with mycologically confirmed dermatophyte infections	N=137 16 weeks	Primary: Clinical response and mycological response	Primary: Clinical response was observed in 20 of 21 patients in the ketoconazole group compared to 9 of 11 in the griseofulvin group. Mycological response was better in the ketoconazole group compared to the griseofulvin group. In the ketoconazole group, 61% achieved remission compared to 39% in the griseofulvin group (P=0.02). In the ketoconazole group, 9% of patients relapsed compared to 43% in the griseofulvin group (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Stratigos et al.[47] (1983) Ketoconazole 200 mg daily until negative culture or 6 weeks vs griseofulvin 500 mg daily until negative culture or 6 weeks	DB, RCT Patients with clinical symptoms and cultures for dermatophytes	N=50 6 weeks	Primary: Cure rate (no symptoms and negative culture results)	Primary: After 2 weeks of treatment, 50% of patients in the ketoconazole group and 25% in the griseofulvin group had negative cultures and this difference was not statistically significant between groups. At 3 weeks, 88.5% of patients in the ketoconazole group and 66.6% in the griseofulvin group had negative cultures and this difference was not statistically significant between groups. There was no significant difference in cure rates between groups.
Tanz et al.[48] (1988) Ketoconazole 3.3-6.6 mg/kg/day for 12 weeks vs griseofulvin 10-20 mg/kg/day for 12 weeks	DB, RCT Patients 2-16 years of age with tinea capitis or mycological evidence of dermatophyte infection of the scalp	N=79 12 weeks	Primary: Clinical response (success=clinical improvement and negative cultures), mycological response, symptom severity score	Primary: Treatment success was observed in 73% of patients in the ketoconazole group and in 96% of patients in the griseofulvin group (P<0.10). There were no significant differences in symptom severity scores between groups (P>0.20). There were no significant differences between groups in mycological response (P<0.90).
Legendre et al.[49] (1980) Ketoconazole 200 mg daily for 28-60 days vs griseofulvin ultramicrosize 250	DB, RCT Patients with microscopically confirmed dermatophyte infection of the skin	N=58 28-day posttreatment follow-up	Primary: Response to therapy (cure= clearance of lesions and negative culture), relapse rates	Primary: Cure was obtained in 38% of patients in the ketoconazole group and 24% of patients in the griseofulvin group after 4 weeks of therapy. After 60 days of therapy, cure was obtained in 83% of ketoconazole patients and 32% of griseofulvin patients (P<0.001). Of the patients cured after 4 weeks of treatment, none of the ketoconazole patients relapsed and all of the griseofulvin patients relapsed (P=0.001). Of all the patients cured regardless of duration of therapy, 7% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg daily for 28-60 days				ketoconazole patients relapsed within 28 days compared to 80% in the griseofulvin group (P=0.006).
Gan et al.[50] (1987) Ketoconazole 5 mg/kg/day until clearance of lesions and negative culture or for 6 months vs griseofulvin 15 mg/kg/day until clearance of lesions and negative culture or for 6 months	RCT Patients 1-12 years of age with a diagnosis of tinea capitis	N=63 6 months	Primary: Negative cultures, relapse rates	Primary: After 1 month of therapy, fungal cultures were negative in 69% of patients treated with griseofulvin and 29% of patients treated with ketoconazole (P<0.01). This statistical difference persisted throughout the follow-up period. At the end of 12 weeks of therapy, 4% of griseofulvin patients continued to have positive cultures compared to 26% in the ketoconazole group. Seven patients (1 in the griseofulvin group and 6 in the ketoconazole group) reverted to negative samples between the 12th and 26th week of treatment. The median time from initiation of therapy to negative culture was significantly longer in the ketoconazole group compared to the griseofulvin group (8 weeks and 4 weeks, respectively, P<0.01).
Martinez-Roig et al.[51] (1988) Ketoconazole 100 mg daily divided every 12 hours until lesions had cleared and negative culture was obtained vs griseofulvin 350 mg daily every 12 hours until lesions	DB, RCT Patients 3 months to 14 years of age with dermatophyte infections who had not received previous antifungal therapy	N=47 2 week posttreatment follow-up	Primary: Response to therapy (clinical cure=clearance of lesions and mycological cure= negative culture), time to clinical cure and negative culture	Primary: After 6 weeks of therapy, clinical and mycological cure or improvement was seen in 92% of patients treated with ketoconazole and 76% of patients treated with griseofulvin. The time to clinical cure and negative cultures was shorter for patients treated with ketoconazole compared to griseofulvin for tinea capitis and shorter for griseofulvin compared to ketoconazole for tinea corporis, though no significant difference was observed in overall response to therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
had cleared and negative culture was obtained				
Tanz et al.[52] (1985) Ketoconazole 200 mg daily vs griseofulvin 500 mg daily	DB, RCT Children 2-16 years of age with mycologically proven tinea capitis	N=22 6 weeks	Primary: Symptom severity score, mycological response (negative cultures)	Primary: The total severity scores decreased in all patients during the course of the study (P<0.05 compared to baseline) and the decrease was similar between groups (P=0.62). After 6 weeks of therapy, 57% of patients in each group were culture negative.
Yazdanpanah et al.[118] (2007) Ketoconazole 400 mg orally as a single dose vs fluconazole 300 mg orally as a single dose, repeated after 2 weeks	OL Patients with extensive pityriasis versicolor	N=90 1 month	Primary: Clinical evaluation for extension and localization of lesions, hyperhidrosis, and greasiness of the skin	Primary: The improvement rate for ketoconazole (87.9%) was not significantly different from fluconazole (81.5%; P=0.37). Equal improvement response was detected in all over areas of the body except forearms involvement, which showed better results in ketoconazole rather than fluconazole treatment group (P=0.049). Total improvement rate did not show any relation to individual characteristics such as age, gender, hyperhidrosis, greasiness of the skin and body involved area (P=0.520, 0.407, 0.614, 0.083, 0.897). Adverse reactions to treatments were seen in three patients (9.09%) in ketoconazole treatment group (flatulence, urine color change and itching) and four patients (14.8%) in the fluconazole treatment group (flatulence, urticaria, exertional dyspnea and perspiration). There was not any significant correlation between presence of side effects and the patient's age (Chi-square: P=0.500).
Onychomycosis				
Ginter et al.[92] (1998) Itraconazole 400	OL Patients with toenail onychomycosis	N=354 10 months	Primary: Clinical cure (complete clearance or	Primary: Clinical cure was achieved in 64% of patients with proximal nail involvement in the big toenails, 77% of patients with proximal nail involvement in other toenails, and in 87% of patients without proximal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg daily for 1 week per month for 3 months			clearance with a few small residual lesions), mycological cure (negative culture)	nail involvement. Mycological cure was achieved in 77% of the patients who were examined (197).
Odom et al.[93] (1997) Itraconazole 200 mg twice daily for 1 week each month for 2 months vs placebo	DB, MC, PC, RCT Patients 18-70 years of age with clinically and mycologically diagnosed fingernail onychomycosis	N=73 24 weeks	Primary: Clinical response (success=cleared or markedly improved nail involvement), mycological response (success= negative culture)	Primary: Significantly more patients in the itraconazole group achieved clinical success compared to the placebo group (77% compared to 0%, P<0.001). Significantly more patients in the itraconazole group achieved mycological success compared to the placebo group (73% and 13% respectively, P<0.001). The proportion of patients achieving overall success (clinical and mycological success) was significantly greater in the itraconazole group compared to the placebo group (68% and 0% respectively, P<0.001).
Haneke et al.[94] (1998) Itraconazole 400 mg/day for 1 week every 4 weeks for 3 months in patients with toenail or fingernail onychomycosis (Group A) vs itraconazole 400 mg/day for 1 week per month for 2 months in patients with fingernail onychomycosis	MC, RCT Patients with onychomycosis of the fingernail, toenail, or both	N=683 18 weeks posttreatment follow-up	Primary: Clinical cure rates, mycological cure rates (undefined)	Primary: Clinical and mycological cure rates at the end of the study were 89% and 68.4% respectively for toenails, 91.4% and 85.3% respectively for fingernails in Group A, and 84.4% and 77.1% respectively for Group B fingernails.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Group B)				
Korting et al.[95] (1993) Itraconazole 100 mg daily for up to 18 months vs griseofulvin ultramicrosize (UMSG) 660 mg daily for up to 18 months vs griseofulvin ultramicrosize (UMSG) 990 mg daily for up to 18 months	OL, RCT Patients with clinically confirmed tinea unguium of the toenails, fingernails, or both	N=109 18 months	Primary: Clinical response, compliance, adverse effects	Primary: There was no significant difference in the cure or partial cure rates between the USMG 660-mg, USMG 990-mg, and itraconazole groups (6%, 14%, and 19% respectively, P=0.2097). There was no significant difference in the rates of marked improvement between the USMG 660-mg, USMG 990-mg, and itraconazole 100-mg groups (36%, 44%, and 39% respectively). No significant difference in compliance was observed between groups. Itraconazole was significantly better tolerated compared to both USMG groups (P<0.0322).
Haugh et al.[96] (2002) Itraconazole 200 mg daily or 400 mg intermittently (for 1 of every 4 weeks) for 3 or 4 months vs griseofulvin 500 mg or 1,000 mg	MA Patients diagnosed with onychomycosis	N=2,063 3-11 months	Primary: Mycological cure at the end of the studies (negative microscopy or culture) Secondary: Negative microscopy or culture at specified time points	Primary: <u>Terbinafine vs placebo (3 trials)</u> After 12 weeks, a significant advantage in mycological cure rates was seen in favor of the terbinafine group compared to the placebo group. <u>Terbinafine vs itraconazole (4 trials)</u> At the end of the study periods, a statistically significant advantage in achieving negative culture and microscopy was seen in favor of terbinafine compared to itraconazole. No significant differences in tolerability were reported. <u>Terbinafine vs griseofulvin (2 trials)</u> Significantly higher rates of negative microscopy and culture were observed in the terbinafine groups at week 24 compared to the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for 3 months or 11 months vs terbinafine 250 mg daily for 3 or 6 months vs placebo				griseofulvin groups.
Brautigam[97] (1998) Itraconazole 200 mg daily for 12 weeks vs terbinafine 250 mg daily for 12 weeks	DB, MC, PG, RCT Patients 18 years of age and older with a clinical diagnosis of distal subungual or proximal onychomycosis of the toenails	N=195 52 weeks	Primary: Mycologic cure (culture negative for dermatophytes and hyphae), clinical efficacy (length of unaffected area on the target nail)	Primary: Significantly more patients in the terbinafine group had experienced mycologic cure (81.4%) compared to the itraconazole group (63.1%, P<0.01) at week 52. At week 52, 91.9% of cultures were negative for dermatophytes in the terbinafine group compared to 66.6% in the itraconazole group (P<0.0001). The mean time to the first negative culture was significantly shorter in the terbinafine group (8.52 weeks) compared to the itraconazole group (11.64 weeks, P<0.05). Terbinafine was significantly more effective in increasing the length of unaffected nail compared to itraconazole. At week 52, a significantly lower number of patients in the terbinafine group had >60% of the nail plate affected (3.5% of patients) compared to the number in the itraconazole group (15.5% of patients, P<0.05).
Evans et al.[98] (1999) Itraconazole 200 mg daily for 1 week every 4	DB, MC, PG, RCT Patients 18-75 years of age with a clinical diagnosis of onychomycosis of	N=496 72 weeks	Primary: Mycologic cure (negative results on microscopy and culture)	Primary: Mycologic cure rates were significantly higher in both terbinafine groups (81% and 80% respectively) compared to the itraconazole groups (41% and 53% for the 3-cyle and 4-cycle itraconazole groups respectively, P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks for 12 or 16 weeks vs terbinafine 250 mg daily for 12 or 16 weeks	the toenail confirmed by positive results on mycologic cure and microscopy		Secondary: Clinical cure (100% toenail clearing), complete cure (mycologic and clinical cure), clinical effective-ness (mycologic cure and at least 5 mm of new clear toenail growth), and global assessments by physician and patient	Secondary: Clinical cure rates were significantly higher in the terbinafine groups compared to the itraconazole groups (P<0.0022). Complete cure rates were significantly higher in the continuous terbinafine group compared to both itraconazole groups (P<0.0044). Clinical effectiveness and global assessments were significantly higher for the continuous terbinafine groups compared to the itraconazole groups (P<0.0001).
Degreef et al.[99] (1999) Itraconazole 200 mg daily for 12 weeks vs terbinafine 250 mg daily for 12 weeks	DB, MC, PG, RCT Patients 18-65 years of age with clinically suspected and microscopically and culturally proven onychomycosis of the toenail	N=297 36 weeks	Primary: Mycologic cure (culture negative) Secondary: Investigator's global clinical evaluation of response to treatment, percentage of total affected nail area, total number of infected nails, signs and symptoms of onycholysis, hyperkeratosis, paronychial inflammation and discoloration	Primary: A similar number of patients were mycologically cured (79 in the terbinafine group and 78 in the itraconazole group). Secondary: Clinical response rates were similar between the groups (P<0.1). Complete clinical cure rates were similar between the groups. The mean percentage of affected nail area and the mean number of nails infected decreased similarly in the two groups. Signs and symptoms of infections improved comparably in the two groups.
Gupta et al.[100]	CS, PRO, RCT, SB	N=101	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Itraconazole 200 mg twice daily for 1 week given as 3 pulses vs terbinafine 250 mg daily for 12 weeks	Patients 60 years of age and older with dermatophyte onychomycosis of at least 1 great toe	18 months	Mycologic cure (negative cultures), clinical efficacy (mycologic cure and either clinical cure or reduction of involved nail plate to 10% or less)	At month 18, the mycologic cure rate in the terbinafine group was 64% and 62.7% in the itraconazole group. No significant difference was found between groups. At month 18, clinical efficacy was 62% in the terbinafine group and 60.8% in the itraconazole group. No significant difference was found between groups.
Sigurgeirsson et al.[101] (1999) Itraconazole 400 mg daily for 1 week every 4 weeks for 12 (3 cycles) or 16 (4 cycles) weeks vs terbinafine 250 mg daily for 12 or 16 weeks	DB, PRO, RCT Patients 18-75 years of age with onycho-mycosis of the toenail confirmed by culture finding infection with a dermatophyte	N=158 72 weeks	Primary: Proportion of patients who remained mycologically cured (negative culture) at the end of follow-up without requiring continued treatment with terbinafine Secondary: Clinical cure (100% normal-appearing nail), complete cure (mycologic plus clinical cure), clinical and mycologic relapse over time, mycologic and clinical cure over time, effect of	Primary: Significantly more patients treated with terbinafine were mycologically cured at the end of the study compared to patients treated with itraconazole (46% compared to 13%, P<0.001). Secondary: Significantly more patients treated with terbinafine were clinically cured at the end of the study compared to patients treated with itraconazole (42% compared to 18%, P<0.002). Significantly more patients in the terbinafine group maintained complete cure at the end of the study compared to patients in the itraconazole group (P<0.005). At the end of the study, significantly fewer terbinafine patients had relapsed mycologically compared to itraconazole patients (23% compared to 53%, P<0.01). At the end of the study, significantly fewer terbinafine patients had relapsed clinically compared to itraconazole patients (21% compared to 48%, P<0.05). For patients who originally received terbinafine and subsequently received a second course of treatment with terbinafine after 18 months, 92% achieved mycologic cure compared to 85% of those originally treated with itraconazole.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			subsequent terbinafine treat-ment on clinical and mycologic outcome	Similar results were seen with clinical cure rates: it was achieved in 76% of patients originally treated with terbinafine and 77% of patients originally treated with itraconazole.
Sigurgeirsson et al.[102] (1999) Itraconazole 400 mg/day for 1 week every 4 weeks for 12 weeks (group I_3) or 16 weeks (group I_4) vs terbinafine 250 mg daily for 12 weeks (group T_{12}) or 16 weeks (group T_{16})	DB, MC, PG, RCT Patients 18-75 years of age with distal subungual or total dystrophic onychomycosis of the toenails confirmed mycologically	N=507 72 weeks	Primary: Mycological cure (negative microscopy and cultures) Secondary: Clinical cure (100% toenail clearing), complete cure (mycological and clinical cure), clinical efficacy (mycological cure and at least 5 mm of new clear toenail growth), global assessment of efficacy by patient and physician	Primary: Mycological cure rates were 75.7% in the T_{12} group, 80.8% in the T_{16} group, 38.3% in the I_3 group and 49.1% in the I_4 group. Results were statistically significant in favor of the terbinafine regimens (P<0.0001). Secondary: Clinical cure was 53.6%, 60.2%, 31.8%, and 32.1% for the T_{12}, T_{16}, I_3, and I_4 groups respectively, and all significantly favored the terbinafine regimens (P<0.002). Complete cure rates were 45.8%, 55.1%, 23.4%, and 25.9% for the T_{12}, T_{16}, I_3, and I_4 groups respectively, and all significantly favored the terbinafine regimens (P<0.0007). Clinical efficacy rates significantly favored the terbinafine regimens (P<0.0001). Global assessment of efficacy by patients was very good or excellent in 78.9%, 78.8%, 43.9%, and 52.3% of patients in the T_{12}, T_{16}, I_3, and I_4 groups, respectively, and these assessments statistically favored the terbinafine regimens (P<0.0001). Global assessment of efficacy by physicians was very good or excellent in 78.9%, 78.8%, 43.9%, and 52.3% of patients in the T_{12}, T_{16}, I_3, and I_4 groups, respectively, and these assessments statistically favored the terbinafine regimens (P<0.0001).
Heikkila et al.[103] (2002) Itraconazole 400 mg daily for 1 of every 4 weeks for	DB, MC, RCT Finnish participants 18-75 years of age with a clinical diagnosis of	N=76 4 years	Primary: Mycologic cure (microscopy and culture negative), clinical cure (100% clearing of all	Primary: At 4 years, terbinafine was shown to be more effective than itraconazole. At 4 years, negative microscopy and culture remained unchanged in the terbinafine group treated for 16 weeks, but fell to <50% in all other groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12 (3 cycles), or 16 (4 cycles) weeks vs terbinafine 250 mg daily for 12 or 16 weeks	onychomycosis of the toenail confirmed by culture		toenails), complete cure (mycologic and complete cure)	At 4 years, clinical and complete cure rates in the terbinafine group treated for 16 weeks was better than the rates seen at 72 weeks (78% compared to 50%), but remained unchanged or worsened in all other groups.
De Backer et al.[104] (1998) Itraconazole 200 mg daily for 12 weeks vs terbinafine 250 mg daily for 12 weeks	DB, RCT Patients 18 years of age and older with clinically suspected subungual dermatophyte infections confirmed by microscopy and culture	N=372 48 weeks	Primary: Percentage of patients with negative culture at week 48, length of healthy nail, hyperkeratosis, onycholysis, paronychial inflammation, investigator and patient assessment of efficacy of treatment	Primary: At week 48, significantly more patients in the terbinafine group had negative microscopy results (77.9%) compared to the itraconazole group (55.4%, P<0.0001). At week 48, significantly more patients in the terbinafine group had negative dermatophyte culture results (84%) compared to the itraconazole group (64.3%, P<0.0001). At week 48, significantly more patients in the terbinafine group had negative mycology results (73%) compared to the itraconazole group (45.8%, P<0.0001). At week 48, patients in the terbinafine group had significantly more healthy nail in the big toe compared to the itraconazole group (8.1 mm and 6.4 mm, respectively, P=0.026). At week 48, onycholysis score significantly favored terbinafine compared to itraconazole (P=0.001). There was no significant difference in hyperkeratosis scores between groups (P=0.27). Paronychial inflammation was absent in the majority of patients in both groups. The global clinical evaluation of the target nail at week 48 was significantly higher in the terbinafine group (cleared or minimal symptoms) compared to the itraconazole group (76.2% and 58.1%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				respectively, P=0.001).
De Backer et al.[105] (1996) Itraconazole 200 mg daily for 12 weeks vs terbinafine 250 mg daily for 12 weeks	DB, RCT Patients with a clinical diagnosis of toenail onychomycosis	N=372 48 weeks	Primary: Clinical symptoms, rate of negative mycology (negative microscopy and negative culture)	Primary: Clinical symptoms in the target nail improved significantly more in the terbinafine group compared to the itraconazole group (P=0.001). The unaffected nail length for big toes was significantly greater in the terbinafine group compared to the itraconazole group (9.1 mm and 7.7 mm respectively, P=0.0298). Onycholysis was less frequent in the terbinafine group compared to the itraconazole group (P=0.001). No significant difference was seen between groups in hyperkeratosis. Negative mycology was observed in 73% of terbinafine patients compared to 45.8% of itraconazole patients at week 48 (P<0.0001).
Arenas et al.[106] (1995) Itraconazole 200 mg daily for 3 months vs terbinafine 250 mg daily for 3 months	CS, OL, PRO Patients 18 years of age and older with onychomycosis	N=53 9 months	Primary: Culture and potassium hydroxide (KOH) smear results, affected nail area, medical evaluation of treatment (cure, improvement, no changes, or deterioration Secondary: Nail changes, nail growth, patient evaluation of treatment	Primary: At the end of treatment, rates of positive KOH smears were similar between groups (21.7% for itraconazole and 23.5% for terbinafine). At the end of treatment, there was 1 positive culture in the terbinafine group; at the end of follow-up, there was 1 positive culture in the itraconazole group. Both treatment groups showed improvement in nail area affected compared to baseline (P<0.01) and there was no significant difference between groups. There was no significant difference between groups in the medical evaluation of treatment. There was no significant difference in cure and improvement between groups. Secondary: There were no significant differences in nail changes or nail growth between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference between groups in the patients' evaluation of treatment.
Bahadir et al.[107] (2000) Itraconazole 100 mg twice daily for the first week of 3 consecutive months vs terbinafine 250 mg daily for 3 months	RCT Patients with clinically and mycologically confirmed onychomycosis	N=60 24 week posttreatment follow-up	Primary: Therapeutic response (healing, remission, or failure, undefined)	Primary: Healing was achieved in 60% of itraconazole patients and 68.5% of terbinafine patients, remission was achieved in 28% of itraconazole patients and 25.7% of terbinafine patients, and failure was reported in 4% of itraconazole patients and 2.85% of terbinafine patients (P=0.50)
Honeyman et al.[108] (1997) Itraconazole 200 mg daily for 4 months vs terbinafine 250 mg daily for 4 months	DB, MC, PG, RCT Patients with toenail onychomycosis	N=179 12 months	Primary: Clinical response (symptom scores), mycological response (negative culture), clinical global evaluation scores, effectively cured patient scores (ECP, defined as complete mycological cure plus clinical improvement or complete cure)	Primary: At the end of treatment, mycological cure was similar for terbinafine and itraconazole (54.9% and 51.8% respectively). At 12 months, the mycological cure was 95.3% for terbinafine and 84.3% for itraconazole (P=0.04). No significant differences in clinical response were observed between groups at month 4 or 12 (P>0.05). There was no significant difference in the CGE at month 4 or 12 between groups when clinical cure was considered, though when clinical improvement was also considered, terbinafine showed significantly better scores (P<0.02). At 4 months, there was no difference in the proportion of patients considered to be ECP, though at 12 months significantly more patients in the terbinafine group were considered ECP (95.3% and 75.7% respectively, P<0.001).
Brautigam et al.[109] (1995)	MC, RCT	N=170	Primary: Mycological	Primary: Mycological cure rates were 81% in the terbinafine group and 63% in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Itraconazole 200 mg daily for 12 week vs terbinafine 250 mg daily for 12 weeks	Patients with a clinical diagnosis of distal subungual or proximal onychomycosis and a growth of dermatophytes	40 week posttreatment follow-up	response (negative culture), area of unaffected nail	itraconazole group (P<0.01). The length of unaffected nail increased to 9.4 mm in the terbinafine group and to 7.9 mm in the itraconazole group (P<0.05).
Tosti et al.[110] (1996) Itraconazole 400 mg daily for 1 week every month (I) vs terbinafine 250 mg daily (T250) vs terbinafine 500 mg daily for 1 week every month (T500)	OL, RCT Patients with onychomycosis of the toenails or fingernails	N=63 6 month posttreatment follow-up	Primary: Mycological response (not cured, cured with residual malformations, cured without residual malformations)	Primary: At the end of the follow-up period, 76.5% of patients in the T250 group were cured without residual malformations compared to 50% in the T500 group and 38.1% in the I group (P=0.013 between T250 and I). At the end of the follow-up period, significantly more patients in the I group were considered cured with residual malformations compared to those in the T250 group (P=0.013). At the end of the follow-up period, significantly more patients in the I group were considered failures compared to those in the T250 group (P=0.013).
Chang et al.[117] (2007) Itraconazole, fluconazole, terbinafine (with or without topical agents)	MA Patients aged ≥18 years with superficial dermatophytosis (tinea pedis, tinea manus, tinea corpora, and tinea	N=19,298 (122 trials) Variable duration	Primary: Cumulative incidence of patients who withdrew from the study because of adverse reactions Secondary:	Primary: For continuous oral antifungal therapy, the pooled risks of treatment discontinuation because of adverse reactions were 3.44% (95% CI, 2.28%-4.61%) for terbinafine 250 mg/day; 1.96% (95% CI, 0.35%-3.57%) for itraconazole 100 mg/day; 4.21% (95% CI, 2.33%-6.09%) for itraconazole 200 mg/day; and 1.51% (95% CI, 0%-4.01%) for fluconazole 50 mg/day. For intermittent or pulse therapy, the pooled risks of treatment discontinuation because of adverse reactions were 2.09% (95% CI, 0%-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	cruris) or onychomycosis who were receiving oral antifungal therapy for 2 or more weeks		Cumulative incidence of patients stopping treatment because of elevation of serum transaminase levels and cumulative incidence of patients developing elevation of serum transaminase levels during treatment but not requiring discontinuation	4.42%) for terbinafine; 2.58% (95% CI, 1.15%-4.01%) for itraconazole; 1.98% (95% CI, 0.05%-3.92%) for fluconazole 150 mg/week and 5.76% (95% CI, 2.42%-9.10%) for fluconazole 300 to 450 mg/week. Secondary: The incidence of liver injury associated with oral antifungal therapy was less than 2% in general. For the risks of having elevated serum transaminase levels that required treatment termination, the pooled risk estimates for continuous therapy ranged from 0.11% (itraconazole 100 mg/day) to 1.22% (fluconazole 50 mg/day). The pooled risk estimates for pulse therapy ranged from 0.39% (fluconazole 150 mg/week and itraconazole 400 mg/day) to 0.85% (fluconazole 300-450 mg/week). The pooled risks of developing elevated serum transaminase levels not requiring treatment discontinuation was on the order of 1.5% for continuous regimens and 1% for intermittent regimens evaluated.
Empirical Therapy				
Marr et al.[81] (2000) Fluconazole 400 mg daily for 75 days after bone marrow transplant (BMT) vs placebo	DB, PC, RCT Patients 11-65 years of age who were autologous or allogeneic bone marrow transplant recipients	N=300 8 years	Primary: Mortality, cause of death, incidence of invasive fungal infections early (<100 days) and late (>100 days) after BMT	Primary: Survival was significantly better for fluconazole compared to placebo (P=0.0001). The survival benefit of fluconazole was significant for patients receiving allogeneic grafts (P=0.0018) but not for those receiving autologous grafts (P=0.60). The overall incidence of invasive candidiasis was increased in patients in the placebo group compared to the fluconazole group (P<0.001). More patients in the placebo group died of invasive candidiasis early and late after BMT (P<0.0068). The incidence of severe graft versus host disease (GVHD) of the gut was significantly higher in the placebo group (P=0.02).
Slavin et al.[82] (1995)	DB, PC, RCT	N=300	Primary: Incidence of	Primary: Systemic fungal infections occurred in 7% of fluconazole patients and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluconazole 400 mg daily vs placebo	Patients >12 years of age and >34 kg undergoing autologous or allogeneic bone marrow transplantation	110 days post-transplant	systemic fungal infections, incidence of superficial fungal infections, incidence of fungal colonization, incidence of empiric amphotericin B use, survival	18% of placebo patients (P=0.004). No cases of *Candida albicans* infections were seen in the fluconazole group compared to 18 cases in placebo patients (P<0.001). Significantly fewer patients in the fluconazole group experienced superficial fungal infections (P<0.001) and fungal colonization (P=0.037). Significantly fewer patients in the fluconazole group required empiric amphotericin B therapy (P=0.005). Significantly fewer deaths occurred in fluconazole patients up to 110 days posttransplant compared to placebo patients (P=0.004).
Bodey et al.[83] (1990) Fluconazole 50 mg daily vs placebo	DB, PC, RCT Patients with a diagnosis of lymphoma, melanoma, sarcoma, breast carcinoma, or bronchogenic carcinoma	N=146 End of hospitalization or 4 weeks	Primary: Development of oral candidiasis	Primary: Oropharyngeal candidiasis developed in 2% of patients receiving fluconazole and 28% receiving placebo (P=0.0003).
MacMillan et al.[84] (2002) <u>Phase 1</u> Fluconazole 400 mg daily (high dose) until neutrophil engraftment (or 6 mg/kg/day for patients weighing <40 kg) vs	RCT Patients 2-67 years of age who were bone marrow transplantation recipients	N=253 2 week posttreatment follow-up	Primary: Incidence of fungal infection during early and maintenance prophylaxis	Primary: During early prophylaxis, 16% of high-dose patients and 18% of low-dose patients had a post-surveillance culture that was positive for yeast (P=0.35). Superficial fungal infections developed in 16% of the high-dose patients and 18% of the low-dose patients (P=0.66). Systemic fungal infections occurred in 8% of the high-dose patients and 2% of the low-dose patients (P=0.06). There was no significant difference between the low- and high-dose groups in the incidence of systemic candidiasis or aspergillosis (P>0.08). Early prophylaxis was discontinued in 60% of high-dose patients and 59%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluconazole 200 mg daily (low dose) until neutrophil engraftment (or 3 mg/kg/day for patients weighing <40 kg) Engrafted, non-neutropenic patients with no active fungal infection went on to phase 2. Phase 2 Fluconazole 100 mg daily (or 1.5 mg/kg/day if <40 kg) until 100 days posttransplant vs clotrimazole troches 10 mg 4 times daily until 100 days posttransplant				of low-dose patients (P>0.80).There was no significant difference in clinical outcomes between groups (P=0.57). There was no significant difference between groups in rates of fungal colonization at any time during the maintenance prophylaxis (P>0.58). There was no significant difference between groups in survival after maintenance prophylaxis.
Johansen et al.[87] (2002) Fluconazole IV/oral at various doses	MA Patients with cancer complicated by neutropenia	N=3,798 (17 trials) Variable duration	Primary: Mortality, invasive fungal infections, colonization, use of additional antifungal therapy, adverse effects	Primary: No significant difference was observed between fluconazole and amphotericin B with regards to mortality (P>0.1). No significant difference was observed between fluconazole and amphotericin B on the rate of invasive fungal infection (P>0.4).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amphotericin B IV/oral at various doses			leading to discontinuation	No significant difference was observed between fluconazole and amphotericin B on fungal colonization (P>0.3). No significant difference was observed overall between groups in the use of additional antifungal therapy (P>0.1). Significantly more patients receiving amphotericin B dropped out of the study due to adverse effects (P<0.009).
Gotzsche et al.[88] (2002) Fluconazole IV/oral at various doses vs amphotericin B IV/oral at various doses vs amphotericin B liposome IV at various doses vs ketoconazole orally at various doses vs itraconazole orally at various doses	MA Patients with cancer and neutropenia from chemotherapy or bone marrow transplants	N=4,155 (31 trials) Variable duration	Primary: Mortality Secondary: Invasive fungal infections, colonization, use of additional antifungal therapy	Primary: No significant differences were observed between group on mortality (P>0.08). Secondary: Invasive fungal infections decreased significantly with amphotericin B, fluconazole, and itraconazole (P<0.04) but not with miconazole or ketoconazole (P>0.2). Definitions of fungal colonization differed greatly between studies, though the effect of prophylaxis on colonization was significant for amphotericin B, fluconazole, itraconazole, and ketoconazole (P<0.02) but not for miconazole (P=0.8) Significantly more patients who received placebo or no treatment required additional antifungal therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs miconazole orally at various doses vs placebo				
Ito et al.[121] (2007) Fluconazole 200 mg orally once daily vs itraconazole 200 mg orally once daily	MC, RCT Adult patients with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS), receiving conventional chemotherapy as remission-induction or consolidation therapy	N=218 4 weeks	Primary: Frequency of systemic fungal infections	Primary: Among the evaluable patients, 64 (62.1%) of 103 episodes in the itraconazole group developed febrile neutropenia, compared with 73 (68.9%) of 106 episodes in the fluconazole group. In 21 (20.4%) of 103 episodes in the itraconazole group and 20 (18.9%) of 106 episodes in the fluconazole group, intravenous antifungal drugs were empirically used instead of discontinuing the prophylactic use of oral antifungals. According to the diagnostic criteria, 4 possible and no probable cases of systemic fungal infection were noted in the itraconazole group, and 8 possible and 3 probable cases were seen in the fluconazole group. There were no cases of proven systemic fungal infection in either group. In patients receiving remission-induction therapy, probable and possible systemic fungal infections were found in 2 (4.9%) of 41 episodes in the itraconazole group, and 7 (15.9%) of 44 episodes were found in the fluconazole group. The numbers of patients who received consolidation therapy were similar in the 2 groups. Among patients with MDS, there was no episode (0%) of probable or possible systemic fungal infection among 15 episodes in the itraconazole group, whereas 3 episodes (23.1%) of possible infection were noted among 13 episodes in the fluconazole group. In patients with AML, no difference between the 2 groups in the development fungal disease was found.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ullmann et al.[86] (2007) Fluconazole 400 mg orally once daily vs posaconazole 200 mg three times daily	DB, MC, PG, RCT Patients ≥13 years of age, having undergone allogeneic hematopoietic stem cell transplantation and either acute or chronic extensive graft-versus-host disease (GVHD)	N=600 112 days	Primary: Incidence of proven or probable invasive fungal infections Secondary: Incidence of proven or probable aspergillosis, incidence of breakthrough proven or probable invasive fungal infections, mortality, and incidence of adverse events	Primary: At 112 days, posaconazole was found to be as effective as fluconazole in preventing all invasive fungal infections (incidence, 5.3% and 9.0%, respectively; OR, 0.56; 95 % CI, 0.30 to 1.07; P=0.07). Secondary: Posaconazole was more effective than fluconazole in preventing proven or probable invasive aspergillosis (2.3% vs 7.0%, respectively; OR, 0.31; 95% CI, 0.13 to 0.75; P=0.006). There were fewer breakthrough invasive fungal infections in the posaconazole group compared to fluconazole (2.4% vs 7.6%, respectively; P=0.004), particularly for invasive aspergillosis (1.0% vs 5.9%, P=0.001). Overall mortality was similar in the two groups, but the number of deaths from invasive fungal infections was lower in the posaconazole group (1%) compared to the fluconazole group (4%; P=0.046). The incidence of treatment-related adverse events was similar in the two groups (36% in the posaconazole group and 38% in the fluconazole group), and the rates of treatment-related serious adverse events were 13% and 10% in the posaconazole and fluconazole treatment groups, respectively.
Hiramatsu et al.[120] (2008) Fluconazole 400 mg IV daily vs micafungin 150 mg IV daily Patients received treatment within 48 hours of the	RCT, OL Adult patients with a hematological malignancy who were undergoing high-dose combination chemotherapy with autologous or allogeneic hematopoietic stem cell transplantation (HSCT)	N=104 4-week posttreatment follow-up	Primary: Treatment success (defined as the absence of proven, probable, or suspected systemic fungal infection through the end of prophylaxis and as the absence of a proven or probable systemic fungal infection	Primary: The overall treatment success rate for patients in the micafungin arm was comparable to that in the fluconazole arm (94.0% and 88.0%, respectively; 95% CI, -5.4 to 17.4; P=0.295). Suspected invasive fungal infections (IFIs) were reported to occur in 4% of patients in the micafungin arm and 12% of patients in the fluconazole arm (P=0.14). More fluconazole-treated patients received empirical antifungal therapy compared with micafungin-treated patients during the post-treatment period only (12.0% vs 4.0%; P=0.14), although there was no significant difference. In total, 4.0% of micafungin-treated patients and 1.0% of fluconazole-treated patients died during course of the study. None of the deaths were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
transplant-related conditioning regimen.			through the end of the 4-week posttreatment period)	related to the study drug.
Aydemir et al.[135] (2011) Fluconazole 3 mg/kg every 3 days vs nystatin 100,000 units every 8 hours vs placebo	RCT Very-low birth weight infants admitted to the NICU	N=278 Treatment from birth to day 30 (or 45 if <1,000 g at birth)	Primary: Prevention of fungal colonization and infection Secondary: Incidence of bacterial sepsis, necrotizing enterocolitis, threshold retinopathy of prematurity requiring surgery, severe intraventricular hemorrhage, bronchopulmonary dysplasia and mortality	Primary: Fungal colonization occurred less frequently in the fluconazole (10.8%) and nystatin (11.7%) groups than in the control group (42.9%; P<0.001). Invasive fungal infection was less frequent in the fluconazole (3.2%) and nystatin groups (4.3%), as compared with in the control group (16.5%; P<0.001). Secondary: There were no significant differences in secondary outcomes. No serious adverse effects of the fluconazole or nystatin therapy were documented.
Vehreschild et al.[131] (2009) Itraconazole vs caspofungin Study medications were dosed at the physician's	OBS Neutropenic patients with cancer and invasive fungal disease (IFD)	N=77 Variable duration	Primary: Evidence of IFD and mortality	Primary: The incidence of breakthrough IFD after secondary prophylaxis was similar in both groups (32.1% and 31.9%). A trend towards fewer proven or probable breakthrough IFD events in the itraconazole group was not significant (29% and 17%). Overall survival favored the itraconazole group, but this trend was not significant (75% and 89%). Death was attributed to IFD in 3.6% of patients receiving caspofungin and 4.3% of patients in the itraconazole group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
discretion.				
Sánchez-Ortega et al.[126] (2011) Itraconazole 200 mg IV/PO BID for 2 days, then 200 mg daily vs posaconazole 200 mg PO TID	OBS Adult patients receiving antifungal prophylaxis for a first allogeneic bone marrow transplant	N=49 100 days	Primary: Incidence of probable or proven breakthrough invasive fungal disease (IFD) Secondary: Probabilities of FFS and OS	Primary: The cumulative incidence of breakthrough proven or probable IFD during the 100-day study period was significantly lower in patients receiving posaconazole prophylaxis than in patients receiving itraconazole (0% vs 12%; P=0.04). Secondary: Patients receiving posaconazole had a significantly higher FFS (91% vs 56%; P=0.003) and OS (91% vs 63%; P=0.011) than patients who received itraconazole.
Cornely et al.[85] (2007) Posaconazole 200 mg orally three times daily vs fluconazole 400 mg orally once daily or itraconazole 200 mg orally twice daily Patients unable to tolerate the oral study drug could receive IV prophylaxis at the same dose for ≤3 days per	MC, RCT Patients ≥13 years of age with acute myelogenous leukemia or the myelodysplastic syndrome and anticipated neutropenia resulting from remission-induction chemotherapy	N=602 12 weeks	Primary: Incidence of proven or probable invasive fungal infections during the prophylactic treatment phase Secondary: Incidence of invasive aspergillosis, incidence of invasive fungal infection within 100 days after randomization, survival, and adverse events	Primary: Invasive fungal infections were reported in 2% of patients in the posaconazole group and 8% of patients in the fluconazole or itraconazole groups (95% CI, –9.7 to –2.5; P<0.001). Secondary: Significantly fewer patients in the posaconazole group had invasive aspergillosis as compared to patients receiving fluconazole or itraconazole (1% vs 7%, respectively P<0.001). During the 100-day period after randomization, 14 of 304 patients (5%) in the posaconazole group had a proven or probable fungal infection, as compared with 33 of 298 patients (11%) in the fluconazole or itraconazole group (P=0.003). The mean (±SD) time to invasive fungal infection was 41±26 days in the posaconazole group and 25±26 days in the fluconazole or itraconazole group (P=0.003). Of the 304 patients in the posaconazole group, 49 (16%) died during the study period, as did 67 of 298 patients (22%) in the fluconazole or itraconazole group (P=0.048); 44 patients (14%) and 64 patients (21%), respectively, died within 100 days. Survival was significantly longer

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chemotherapy cycle.				among recipients of posaconazole than among recipients of fluconazole or itraconazole (P=0.04). Serious adverse events related to treatment were reported by 19 patients (6%) in the posaconazole group and 6 patients (2%) in the fluconazole or itraconazole group (P=0.01). The most common treatment-related adverse events in both groups were gastrointestinal disturbances.
Mandhaniya et al.[133] (2011) Voriconazole 6 mg/kg/dose for 2 doses, then 4 mg/kg/dose BID vs amphotericin B 0.5 mg/kg/day 3 times per week	RCT, OL, SC Pediatric patients with ALL or AML undergoing induction chemotherapy	N=100 Variable duration	Primary: Failure of antifungal prophylaxis and completion of antifungal protocol	Primary: In the voriconazole arm, 28% of patients failed antifungal prophylaxis compared to 34% of patients in the amphotericin arm (P=0.66). There was no significant difference in the proven, possible, or probable fungal infections in the two study arms. There was a significant increase in adverse events in the amphotericin arm (P<0.01).
Wingard et al.[136] (2010) Voriconazole was 200 mg twice daily vs fluconazole 400 mg once daily	RCT, DB, MC Patients ≥2 years of age undergoing allogeneic HCT after a myeloablative conditioning regimen receiving HLA-matched hematopoietic grafts	N=600 180 days	Primary: Fungal-free survival (FFS) at 180 days posttransplant Secondary: Incidence of IFIs, time to IFI, 6-month and 1-year relapse-free survival (RFS) and OS, frequency, time to, and duration of empiric antifungal therapy,	Primary: FFS rates were similar at 180 days: 75% and 78% for fluconazole and voriconazole, respectively (P=0.49). FFS rates were similar at 12 months: 65% and 64% for fluconazole and voriconazole, respectively (P=0.95). Secondary: The cumulative incidence rates of IFIs (proven, probable, and presumptive) were 11.2% and 7.3% for fluconazole and voriconazole, respectively at 180 days (P=0.12). The cumulative incidence rates of IFIs were 13.7% and 12.7% for fluconazole and voriconazole, respectively at 12 months (P=0.59). There was no difference in other outcomes between the two treatments.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			frequency of severe adverse events, and incidence of acute and chronic GVHD	
Mattiuzzi et al.[130] (2011) Voriconazole 400 mg IV every 12 hours for 2 doses, followed by 300 mg every 12 hours vs itraconazole 200 mg IV BID for 2 days, followed by 200 mg IV daily	OL, RCT, SC Adults with newly diagnosed AML or high-risk MDS undergoing first-line induction therapy or first salvage therapy	N=127 Up to 42 days	Primary: Completion of prophylaxis without the development of invasive fungal infection (IFI); mortality	Primary: None of the patients receiving voriconazole developed proven or probable IFI, whereas two (4%) of the patients receiving itraconazole developed IFI (P=0.17). Six patients (8.4%) in the voriconazole group and 6 patients (11.5%) in the itraconazole group died during the study period (P=0.792).
Marks et al.[138] (2011) Voriconazole 6 mg/kg IV every 12 hours for 1 day, then 200 mg orally twice daily vs itraconazole 200 mg IV every 12 hours for 2 days, then 200 mg orally twice daily	RCT, OL, MC Patients ≥12 years of age and received sibling or unrelated donor alloHCT for acute leukemia, myelodysplasia, transformed chronic myeloid leukemia, or failed lymphoma therapy	N=489 1 year	Primary: Success of prophylaxis, tolerability, survival to day 180 without proven/probable invasive fungal infections (IFI)	Primary: Success of antifungal prophylaxis at day 180 was demonstrated in 48.7% of voriconazole patients and 33.2% of itraconazole patients (95% CI, 7.7-25; P=0.0002). At day 100, the adjusted difference in success of prophylaxis was 15.4% (95% CI, 6.6–24.2; P<0.01) favoring voriconazole (54.0% vs 39.8% respectively). The difference in success rates between treatments did not vary across randomization strata (day 100, P=0.29; day 180, P=0.41). The proportion of patients who completed ≥100 days of study drug prophylaxis was 53.6% for voriconazole versus 39.0% for itraconazole (95% CI of difference, 5.6–23.5; P<0.01). Median total durations of study drug treatment were 96 and 68 days respectively (P<0.01). The most common treatment-related adverse events were vomiting (16.6%), nausea (15.8%) and diarrhea (10.4%) for itraconazole, and hepatotoxicity/liver function abnormality (12.9%) for voriconazole. More

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Study medications were given for 100 to 180 days.				itraconazole patients received other systemic antifungals (41.9% vs 29.9%; P<0.01). Kaplan–Meier estimates of survival at day 100 (91.9% for voriconazole, 92.3% for itraconazole) and day 180 (81.9% for voriconazole, 80.9% for itraconazole) were similar. One-year survival rates were 73.5% and 67.0% for voriconazole and itraconazole respectively (P=0.17; log-rank test). The hazard ratio for death in the voriconazole group compared with the itraconazole group was 0.79 (95% CI, 0.56–1.11). A total of 1.3% of voriconazole patients developed a proven or probable IFI during the study period, compared with 2.1% of itraconazole patients (95% CI, 3.1 to 1.6; P=0.54).
Chabrol et al.[134] (2010) Voriconazole or caspofungin as primary prophylaxis vs no prophylaxis	RETRO Patients receiving first induction chemotherapy for AML of ALL	N=257 Variable duration	Primary: Cumulative incidence of invasive aspergillosis (IA) Secondary: Overall survival, survival at 100 days after chemotherapy, IA-specific survival, mean duration of hospitalization, cumulative incidence of adverse events	Primary: The cumulative incidence of IA was significantly lower in the prophylaxis group than in the non-prophylaxis group (4.5% and 12.4%, respectively; P=0.04). Secondary: The 3-month mortality rate was 28%. The median overall survival of patients with IA was significantly shorter than in patients without IA (215 versus 782 days; P=0.0008). There was no significant difference in 100-day survival between the two groups (83% in the prophylaxis group and 82% in the non-prophylaxis group). The 1-year survival rate was 53% in the prophylaxis group and 65% in the non-prophylaxis group (P=NS).
Clarkson et al.[90] (2007) Medications absorbed from the gastrointestinal (GI) tract	MA Patients with cancer receiving chemotherapy, radiation, or both	N=4,226 (28 trials) Variable duration	Primary: Prevention of oral candidiasis Secondary: (If available) relief of pain, amount of	Primary: Drugs absorbed or partially absorbed from the GI tract were found to significantly decrease the incidence of oral candidiasis compared to non-absorbed drugs (P<0.016). Drugs absorbed or partially absorbed from the GI tract were found to significantly decrease the incidence of oral candidiasis compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(fluconazole, ketoconazole, itraconazole) vs medications partially absorbed from the GI tract (miconazole, clotrimazole) vs medications not absorbed from the GI tract (amphotericin B, nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin) vs placebo or no treatment			analgesia, relief of dysphagia, incidence of systemic infection, duration of hospital stay, cost of oral care, patient quality of life, death, use of empirical antifungal therapy, toxicity, compliance	placebo or no treatment (P<0.004). Secondary: Significantly fewer patients who were treated with drugs absorbed from the GI tract required empiric antifungal therapy compared to placebo or no treatment (P=0.04). This effect was not seen in patients treated with drugs which are partially absorbed (P=0.4). This outcome was not analyzed in any study on non-absorbable drugs. No significant differences were observed between groups in any other secondary endpoint.
Miscellaneous Infections				
Anaissie et al.[79] (1996) Fluconazole 400 mg daily IV for 5 days, then orally thereafter	MC, PRO, RCT Patients 13 years of age and older with documented or presumed fungal infections	N=164 End of therapy	Primary: Response rates (response= disappearance of all clinical and laboratory indicators of infection), survival	Primary: Overall response rates were not significantly different between groups (P>0.26). Median time to defervescence was 5 days in both groups. Median duration of therapy was not statistically different between groups (P=0.80).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amphotericin B 25-50 mg daily IV (non-neutropenic patients) or 0.67 mg/kg/day (neutropenic patients)			rates, adverse events	There were no significant differences in survival rates between groups The incidence of adverse events was significantly higher in the amphotericin B group compared to the fluconazole group (P<0.0001).
Violaris et al.[129] (2010) Fluconazole 4 mg/kg/day vs nystatin suspension 100,000 units every 6 hours	RCT Pre-term, very low birth weight infants between 3-7 days old admitted to the NICU	N=80 Treatment started during first week of life and continued until full oral feedings attained	Primary: Incidence of systemic fungal infection (SFI)	Primary: SFI developed in 2 infants (5.3%) in the fluconazole group and 6 infants (14.3%) in the nystatin group (RR 0.37; 95% CI, 0.08 to 1.72). There was a significant difference in mortality between groups (fluconazole, 0 deaths; nystatin, 6 deaths; P=0.03).
van't Wout et al.[89] (1991) Itraconazole 200 mg orally twice daily vs amphotericin B 0.6 mg/kg/day IV Some patients treated with amphotericin B also received	MC, RCT Neutropenic patients with proven or highly suspected fungal infections	N=40 Duration of therapy (up to 104 days)	Primary: Response to therapy (at least 50% decrease in size of initial site or severity of infection or resolution of all signs of infection)	Primary: Response to treatment was observed in 63% of itraconazole patients and 56% of amphotericin B patients (P>0.90).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
flucytosine at 150 mg/kg/day. In these cases, the amphotericin B dose was 0.3 mg/kg/day.				
Shikanai-Yasuda et al.[111] (2002) Itraconazole 50 mg to 100 mg daily for 4-6 months vs ketoconazole 200 mg to 400 mg daily for 4-6 months vs sulfadiazine 100 mg to 150 mg/kg/day for 4-6 months	RCT Patients with active para-coccidioidomycosis	N=42 10 months	Primary: Clinical response to therapy, serologic response (lowering of antibody levels)	Primary: Clinical responses were similar between groups. All 3 regimens lowered antibody levels compared to baseline (P=0.0001, 0.017, 0.0012 for itraconazole, ketoconazole, and sulfadiazine, respectively).
Schuler et al.[124] (2007) Itraconazole 200 mg IV every 12 hours for 2 days, then 200 mg once daily vs	RCT, OL Hospitalized adult patients with hematological malignancy treated with myelosuppressive therapy and/or who were stem cell	N=162 28 days	Primary: Permanent discontinuation of study medication due to any adverse event Secondary: Response and success rate for	Primary: Significantly fewer itraconazole patients discontinued treatment due to any adverse event (22.2 vs 56.8% AMB; P<0.0001). The main reason for discontinuation was a rise in serum creatinine (1.2% itraconazole vs 23.5% AMB). Renal toxicity was significantly higher and more drug-related adverse events occurred in the AMB group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amphotericin B (AMB) IV 0.7-1.5 mg/kg/day	transplant recipients with a neutrophil count of $<1.0\times10^9$ cells/l expected to last for at least 7 days from the start of the study medication; fever ≥38 °C not responding to at least 72 h of broad spectrum antibiotics and a life expectancy ≥14 days		both treatment groups	Secondary: Intention-to-treat (ITT) analysis showed favorable efficacy for itraconazole; response and success rates were both significantly higher than for AMB (61.7 vs 42% and 70.4 vs 49.3%, both P<0.0001). Treatment failure was reduced in itraconazole patients (25.9 vs 43.2%), primarily due to better tolerability.
Herbrecht et al.[128] (2010) Posaconazole 800 mg/day vs standard antifungal therapy	RCT Patients with invasive fungal infections refractory to standard antifungal therapy	N=193 12-month follow-up after discharge	Primary: Survival estimates	Primary: Significantly more patients treated with posaconazole were alive at every time point analyzed (days 28-365) than patients treated with standard antifungal medications (P<0.0001). The absolute difference in all-cause mortality ranged from 27.0% to 31.2%. At the last time point (day 365), 41% of patients treated with 800 mg/day of posaconazole remained alive compared to 14% of patients treated with standard antifungal therapy (P<0.0001).
Perfect et al.[80] (2003) Voriconazole 6 mg/kg IV every 12 hours as a loading dose, followed by 4 mg/kg every 12 hours for at least 3 days	RCT, OL Patients with documented invasive fungal infections and evidence of failure, intolerance or toxicity related to other approved therapies or infections with no	N=273 End of therapy	Primary: Global response	Primary: Satisfactory global responses were observed in 50% of the overall cohort, in 47% of patients who failed to respond to other therapies, and 68% of patients with infections with no approved antifungal therapy. In patients with aspergillosis, the efficacy rate was 43.7%. In patients with candidiasis, the efficacy rate was 57.5%. In patients with Cryptococcus, the efficacy rate was 38.9%. In patients with fusariosis, the efficacy rate was 45.5%. In patients with scedosporiosis, the efficacy rate was 30%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients could be switched to oral voriconazole at 200-300 mg twice daily or started on oral voriconazole at this dose.	currently approved therapies (including scedosporiosis and fusariosis)			

Drug regimen abbreviations: BID=twice daily, IV=intravenously, PO=by mouth, PV=intravaginally, QD=once daily
Study abbreviations: AC=active control, CS=comparative study, DB=double blind, DD=double dummy, MA=meta-analysis, MC=multi-center, NC=non-comparative, NI=non-inferiority, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind

Additional Evidence

Dose Simplification:
Itraconazole is said to maintain therapeutic levels in fingernails and toenails for a considerable period of time after systemic therapy. Because of this, pulse dosing with higher daily doses of itraconazole has been used to treat onychomycosis.[98] Several studies have been conducted analyzing the clinical effects of pulse doses of itraconazole compared to continuous dosing of terbinafine for the treatment of this condition.[96,98,100-103] Results indicate that clinical and mycological outcomes are not enhanced as a result of less frequent dosing, and some studies show significantly better results with the use of continuous terbinafine therapy compared to the use of itraconazole in a pulse-dose regimen.[96,98,101-102]

Stable Therapy:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits:
An evidence-based medicine literature search 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 Azoles

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Fluconazole	injection, suspension, tablet	Diflucan®*	$$-$$$$$	$-$$$$
Itraconazole	capsule, solution	Sporanox®*	$$$$$	$$$$$
Ketoconazole	tablet	N/A	N/A	$
Posaconazole	suspension	Noxafil®	$$$$$	N/A
Voriconazole	injection, suspension, tablet	Vfend®*, Vfend IV®	$$$$$	$$$$$

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

X. Conclusions

The azoles are approved to treat a variety of fungal infections.[1-8] All of the products are available in a generic formulation, with the exception of posaconazole. There are many guidelines that define the appropriate place in therapy for the azoles.[10-23] The agent that is recommended is dependent upon the infectious organism being treated and the location of the infection. The azoles are recommended as specific therapy for the treatment of aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcal disease, histoplasmosis, sporotrichosis, tinea capitis, as well as for prophylaxis in patients with chemotherapy-induced neutropenia and hematopoietic stem cell transplantation recipients.[9-16,18-20,23,140]

Clinical trials have demonstrated comparable efficacy among the azoles for the treatment of candidiasis (esophageal, oropharyngeal, and vaginal), cryptococcal disease, dermatophyte infections, as well as for prophylaxis.[43,55,58-63,74-75,86,111,118-119,122,130,136,138] There are relatively few studies that have demonstrated greater efficacy with one azole antifungal agent over another.[56-57,85,126] The azoles have also been shown to be comparable in efficacy to antifungal agents in other classes.[35-38,40-41,45,47,51-52,64-68,76-77,95,99-100,112-116,125,131,133,135]

The azoles are generally well tolerated with gastrointestinal symptoms being the most frequently reported adverse event. Treatment with an azole may lead to hepatic function abnormalities, which range from mild elevations in transaminases to severe hepatotoxicity. There are also numerous drug interactions reported with these agents due to oxidative drug metabolism via the cytochrome P450 enzyme system.

There is insufficient evidence to support that one brand azole 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 azoles 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 azole 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Echinocandins
AHFS Class 081416
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I. Overview

The echinocandins are approved for the treatment of *Candida* infections.[1-6] Caspofungin is also approved for the treatment of invasive aspergillosis in patients who are refractory to, or intolerant of, other therapies. The echinocandins inhibit the synthesis of β (1,3)-D-glucan, an enzyme responsible for the synthesis of an essential component of fungal cell walls.[1-6]

The echinocandins that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The topical antifungals were previously reviewed with the skin and mucous membrane agents (AHFS 840408) and are not included in this review. There are no generic products available. This class was last reviewed in November 2009.

Table 1. Echinocandins Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Anidulafungin	injection	Eraxis®	none
Caspofungin	injection	Cancidas®	none
Micafungin	injection	Mycamine®	none

PDL=Preferred Drug List

The echinocandins 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 FDA-approved indications for the echinocandins 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 anti-infective 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 Echinocandins[1-6]

Organism	Anidulafungin	Caspofungin	Micafungin
Aspergillus species		✔	
Candida species	✔	✔	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Echinocandins

Clinical Guideline	Recommendation(s)
American Thoracic Society (ATS): **Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients[51] (2011)**	<u>Invasive Aspergillosis</u> • When invasive disease is suspected or confirmed, prompt, aggressive antifungal treatment is essential. • Although amphotericin B deoxycholate had historically been the ‘‘gold standard’’ for the treatment of invasive aspergillosis, most clinicians and the most recent IDSA guidelines recommend voriconazole as the primary treatment option. • There are no definitive data or consensus opinions indicating improved efficacy of any of the lipid amphotericin formulations over amphotericin B deoxycholate in the treatment of invasive aspergillosis.

Clinical Guideline	Recommendation(s)

	Thus, the best indication for using a lipid formulation appears to be for reducing renal toxicity to allow the administration of high doses of amphotericin for a prolonged time.
	• Voriconazole has recently emerged as a standard therapy for the treatment of invasive aspergillosis, based on the results of a randomized trial comparing the outcomes to amphotericin B deoxycholate; however, whether outcomes are superior to lipid formulations of amphotericin B has not been determined. In many instances voriconazole may be considered the treatment of choice the patient can be transitioned to oral formulations of this drug.
	• Oral itraconazole is not recommended for initial therapy for invasive aspergillosis. However, after disease progression is arrested with either voriconazole or amphotericin, the patient can be transitioned to oral itraconazole.
	• Caspofungin use in invasive aspergillosis is largely limited to salvage therapy, often in combination with other antifungal agents, after primary therapy with amphotericin-based regimens have failed.
	• There is currently insufficient clinical support to recommend combination therapy, although many clinicians are employing this approach as a ‘‘last option,’’ or in settings of particularly advanced disease.
	<u>Invasive Pulmonary Aspergillosis</u>
	• In patients with invasive pulmonary aspergillosis, the following are recommended:
	  ○ Intravenous voriconazole 6 mg/kg every 12 hours for 1 day, followed by 4 mg/kg every 12 hours until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400–600 mg/day until resolution or stabilization of all clinical and radiographic manifestations OR
	  ○ Intravenous liposomal amphotericin B 3–5 mg/kg/day until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400–600 mg/day until resolution or stabilization of all clinical and radiographic manifestation
	• In patients with invasive pulmonary aspergillosis who have failed front line therapy and are requiring salvage therapy, the following are recommended:
	  ○ Intravenous caspofungin 70 mg on Day 1 and 50 mg/day intravenously thereafter, or intravenous micafungin 100– 150 mg/day until improvement, followed by oral voriconazole 200 mg every 12 hours or oral itraconazole 400–600 mg/day until resolution of disease OR
	  ○ Posaconazole 200 mg four times per day initially, then 400 mg twice daily orally after stabilization of disease
	<u>Chronic Necrotizing Aspergillosis</u>
	• In patients with chronic necrotizing aspergillosis, with mild to moderate disease, voriconazole (200 mg every 12 h) or itraconazole (400–600 mg/d) is recommended until resolution or stabilization of all clinical and radiographic manifestations.
	• If clinically severe, consider beginning therapy of chronic necrotizing aspergillosis with either liposomal amphotericin B or IV voriconazole as described above for invasive disease.
	• In select patients at high risk of invasive fungal infection, some anti-*Aspergillus* prophylaxis is warranted. Data support the use of posaconazole 200 mg orally three times daily until recovery from

Clinical Guideline	Recommendation(s)

	neutropenia and clinical remission is established. Other prophylaxis approaches have utilized itraconazole, micafungin, and inhaled liposomal amphotericin B.
	Candidemia
	• Candidemia should be treated with antifungal agents, selecting one of the following agents: fluconazole, an amphotericin B formulation, an echinocandin, voriconazole, or the combination regimen of fluconazole and amphotericin B.
	• For patients who are clinically stable and have not recently received azole therapy, the following are recommended:
	  o Fluconazole (400 mg/d or ~6 mg/kg/d) OR
	  o Caspofungin (70 mg loading dose day 1, then 50 mg/d) OR
	  o Micafungin (100 mg/d) OR
	  o Anidulafungin (200 mg on day 1, then 100 mg/d).
	• For patients who are clinically unstable and for whom identification of the *Candida* species in the blood is unknown, there is no definitive recommendation. Several options are available and include:
	  o Amphotericin B deoxycholate (0.6–1.0 mg/kg/d) or a lipid formulation of amphotericin B (3–5 mg/kg/d) OR
	  o High-dose fluconazole (800 mg/kg/d or z 12 mg/kg/d) OR
	  o Caspofungin (70 mg loading dose day 1, then 50 mg/d) OR
	  o Micafungin (100 mg/d) OR
	  o Anidulafungin (200 mg on day 1, then 100 mg/d) OR
	  o Voriconazole (6 mg/kg/12 h X 2, then 3 mg/kg/12 h) OR
	  o A combination regimen with fluconazole (800 mg/d) and amphotericin B (0.6– 1.0 mg/kg/d, for the first 5–6 d)
	• For *C. albicans* and also possibly *C. tropicalis*, the drugs of choice are fluconazole (400 mg/d), amphotericin B (0.6–1.0 mg/kg/d), and an echinocandin.
	• For *C. parapsilosis*, the drugs of choice are fluconazole (400 mg/d) or amphotericin B (0.6–1.0 mg/kg/d).
	• For *C. glabrata*, the drugs of choice are an echinocandin or amphotericin B. High-dose fluconazole (800 mg/d) may be a suitable alternative.
	• For *C. krusei*, the drugs of choice are an echinocandin or amphotericin B.
	• For *C. lusitaniae*, fluconazole is the preferred therapy.
	• Lipid formulations of amphotericin B are usually indicated for patients intolerant of, or refractory to, conventional antifungal therapy.

Infectious Diseases Society of America (IDSA): **Treatment of Aspergillosis**[7] **(2008)**	Invasive Pulmonary Aspergillosis • For primary treatment of invasive pulmonary aspergillosis, IV or oral voriconazole is recommended for most patients. For seriously ill patients, the parenteral formulation is recommended. • Liposomal amphotericin B (L-AMB) may be considered as alternative primary therapy in some patients. For salvage therapy, agents include lipid formulations of amphotericin (LFABs), posaconazole, itraconazole, caspofungin, or micafungin. Cutaneous Aspergillosis • Therapy for secondary cutaneous lesions reflects that of disseminated infection, with systemic voriconazole recommended as primary therapy. • Alternative agents include L-AMB, posaconazole, itraconazole, or an echinocandin. Empirical Antifungal Therapy of Neutropenic Patients with Prolonged Fever Despite Antibacterial Therapy and Presumptive Therapy for Invasive

Clinical Guideline	Recommendation(s)
	Aspergillosis • Empirical antifungal therapy with AMB, an LFAB, itraconazole, voriconazole, or caspofungin is recommended for high-risk patients with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy. • Empirical antifungal therapy is not recommended for patients who are anticipated to have short durations of neutropenia (duration of neutropenia, <10 days), unless other findings indicate the presence of an invasive fungal infection.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for the Management of Candidiasis[8] (2009)**	Candidemia in Non-neutropenic Patients • Fluconazole or an echinocandin (caspofungin, micafungin or anidulafungin) is recommended as initial therapy for most adult patients. An echinocandin is preferred for patients with moderately severe to severe illness or for patients who have had recent azole exposure. Fluconazole is recommended for patients who are less critically ill and who have had no recent azole exposure. • Transition from an echinocandin to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *Candida albicans*) and who are clinically stable. • For infection due to *Candida glabrata*, an echinocandin is preferred. Transition to fluconazole or voriconazole therapy is not recommended without confirmation of isolate susceptibility. • For infection due to *Candida parapsilosis*, treatment with fluconazole is recommended. For patients who have initially received an echinocandin, are clinically improved, and whose follow-up culture results are negative, continuing use of an echinocandin is reasonable. Candidemia in Neutropenic Patients • An echinocandin (caspofungin, micafungin or anidulafungin) or LFAmB is recommended for most patients. • For patients who are less critically ill and who have no recent azole exposure, fluconazole is a reasonable alternative. Voriconazole can be used in situations in which additional mold coverage is desired. • For infections due to *C. glabrata*, an echinocandin is preferred. LFAmB is an effective but less attractive alternative. For patients who were already receiving voriconazole or fluconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of the azole to completion of therapy is reasonable. • For infections due to *C. parapsilosis*, fluconazole or LFAmB is preferred as initial therapy. If the patient is receiving an echinocandin, is clinically stable, and follow-up culture results are negative, continuing the echinocandin until completion of therapy is reasonable. For infections due to *C. krusei*, an echinocandin, LFAmB, or voriconazole is recommended. Empirical Treatment for Suspected Invasive Candidiasis in Non-neutropenic Patients • Empirical therapy for suspected candidiasis in non-neutropenic patients is similar to that for proven candidiasis. Fluconazole, caspofungin, anidulafungin, or micafungin is recommended as initial therapy. An echinocandin is preferred for patients who have had recent azole exposure, whose illness is moderately severe or severe, or who are at high risk of infection due to *C. glabrata* or *C. krusei*. • Empirical antifungal therapy should be considered for critically ill patients with risk factors for invasive candidiasis and no other known cause of fever, and it should be based on clinical assessment of risk factors, serologic markers for invasive candidiasis, and/or culture data

Clinical Guideline	Recommendation(s)
	from non-sterile sites. Empirical Treatment for Suspected Invasive Candidiasis in Neutropenic Patients • LFAmB, caspofungin, or voriconazole are recommended. • Fluconazole and itraconazole are alternative agents. • AmB-d is an effective alternative, but there is a higher risk of toxicity with this formulation than with LFAmB. • Azoles should not be used for empirical therapy in patients who have received an azole for prophylaxis. Treatment for Neonatal Candidiasis • Echinocandins should be used with caution and are generally limited to situations in which resistance or toxicity precludes the use of fluconazole or AmB-d. Chronic Disseminated Candidiasis • Fluconazole is recommended for clinically stable patients. LFAmB or AmB-d can be used to treat acutely ill patients or patients with refractory disease. Induction therapy with AmB for 1–2 weeks, followed by oral fluconazole is also recommended. • Anidulafungin, micafungin, or caspofungin are alternatives for initial therapy, followed by oral fluconazole when clinically appropriate. • Therapy should be continued for weeks to months, until calcification occurs or lesions resolve. Premature discontinuation of antifungal therapy can lead to recurrent infection. Osteoarticular *Candida* Infections • For osteomyelitis, fluconazole is recommended at a dosage of 400 mg daily for 6–12 months or LFAmB at a dosage of 3–5 mg/kg daily for at least 2 weeks, followed by fluconazole at a dosage of 400 mg daily for 6–12 months. • Alternatives include an echinocandin or AmB-d at a dosage of 0.5–1 mg/kg daily for at least 2 weeks, followed by fluconazole at a dosage of 400 mg daily for 6–12 months. • For septic arthritis, treatment with fluconazole for at least 6 weeks at a dosage of 400 mg daily or LFAmB at a dosage of 3–5 mg/kg daily for at least 2 weeks, followed by fluconazole at a dosage of 400 mg daily. • Alternatives include an echinocandin or AmB-d at a dosage of 0.5–1 mg/kg daily for at least 2 weeks, followed by fluconazole at a dosage of 400 mg daily for the remainder of therapy. • For infection involving a prosthetic device, device removal is recommended for most cases. Therapy for at least 6 weeks with the above dosages of fluconazole, LFAmB, an echinocandin, or AmB-d is recommended. If the device cannot be removed, chronic suppression with fluconazole is recommended. *Candida* Endophthalmitis • AmB-d combined with flucytosine is recommended for advancing lesions or lesions threatening the macula. Fluconazole is an acceptable alternative for less severe endophthalmitis. • LFAmB, voriconazole, or an echinocandin can be used to treat patients who are intolerant of or experiencing treatment failure with AmB-d in combination with flucytosine or fluconazole. Cardiovascular *Candida* Infections • For native valve endocarditis, LFAmB with or without flucytosine is recommended. Alternatives include AmB-d with or without flucytosine or an echinocandin (caspofungin or anidulafungin). Step-down therapy to fluconazole should be considered among patients with susceptible *Candida* isolates who have demonstrated clinical stability and

Clinical Guideline	Recommendation(s)
	clearance of *Candida* from the bloodstream. Valve replacement is recommended, and treatment should continue for at least 6 weeks after valve replacement and should continue for a longer duration in patients with perivalvular abscesses and other complications. • For prosthetic valve endocarditis (PVE), the recommendations above apply, and suppressive therapy should be lifelong if valve replacement is not possible. • For pericarditis, LFAmB, AmB-d, an echinocandin, or fluconazole for as long as several months, in combination with either a pericardial window or pericardiectomy, is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to AmB or an echinocandin and who are clinically stable. • For myocarditis, treatment as for endocarditis (as stated above) is recommended. • For suppurative thrombophlebitis, catheter removal and incision and drainage or resection of the vein, if feasible, is recommended. LFAmB, AmB-d, fluconazole, or an echinocandin for at least 2 weeks after candidemia has cleared is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to AmB or an echinocandin and who are clinically stable. Resolution of the thrombus can be used as evidence to discontinue antifungal therapy if clinical and culture data are supportive. • For pacemaker and implantable cardiac defibrillator wire infections, removal of the entire device and systemic antifungal therapy with LFAmB with or without flucytosine, AmB-d with or without flucytosine, or an echinocandin is recommended. Step-down therapy to fluconazole should be considered for patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. For infections limited to generators and/or pockets, 4 weeks of antifungal therapy after removal of the device is recommended. For pacemaker and implantable cardiac defibrillator wire infections, at least 6 weeks of antifungal therapy after wire removal is recommended. • For ventricular assist devices that cannot be removed, treatment with LFAmB, AmB-d, or an echinocandin is recommended. After candidemia has cleared and the patient has responded clinically, fluconazole is recommended as step-down therapy. <u>Oropharyngeal Candidiasis</u> • For mild disease, clotrimazole troches, nystatin suspension, or nystatin pastilles for 7–14 days is recommended. • For moderate to severe disease, oral fluconazole for 7–14 days is recommended. • For fluconazole-refractory disease, either itraconazole solution or posaconazole suspension for up to 28 days are recommended. Voriconazole or AmB-d are recommended when treatment with other agents has failed. Intravenous echinocandin or AmB-d can be used in treating patients with refractory disease. <u>Esophageal Candidiasis</u> • Systemic antifungal therapy is always required. Oral fluconazole for 14–21 days is recommended. Intravenous fluconazole, AmB-d, or an echinocandin should be used for patients who cannot tolerate oral therapy. A diagnostic trial of antifungal therapy is appropriate before performing an endoscopic examination. • For fluconazole-refractory disease, itraconazole solution, posaconazole suspension, or voriconazole (administered intravenously or orally) for 14– 21 days is recommended. Micafungin, anidulafungin, or AmB-d

Clinical Guideline	Recommendation(s)
	are acceptable alternatives. Antifungal Prophylaxis for Solid-Organ Transplant Recipients, Patients Hospitalized in Intensive Care Units (ICUs), Neutropenic Patients receiving Chemotherapy, and Stem Cell Transplant Recipients at Risk of Candidiasis • For solid-organ transplant recipients, fluconazole or liposomal AmB (L-AmB) is recommended as postoperative antifungal prophylaxis for liver, pancreas, and small bowel transplant recipients at high risk of candidiasis. • For patients hospitalized in the ICU, fluconazole is recommended for high-risk patients in adult units that have a high incidence of invasive candidiasis. • For patients with chemotherapy-induced neutropenia, fluconazole, posaconazole, or caspofungin is recommended during induction chemotherapy for the duration of neutropenia. Oral itraconazole is an effective alternative, but it offers little advantage over other agents and is less well tolerated. • For stem cell transplant recipients with neutropenia, fluconazole, posaconazole, or micafungin is recommended during the period of risk of neutropenia.
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[9] (2008)**	Mucocutaneous Candidiasis • Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14–21-day course of either fluconazole (oral or IV) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. • Although the echinocandins are effective in treating esophageal candidiasis among HIV-infected patients, oral or IV fluconazole remain the preferred therapies due to a greater relapse rate when compared to fluconazole. • Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. Aspergillosis • Voriconazole is the drug of choice but should be used cautiously with HIV protease inhibitors and efavirenz. Amphotericin B deoxycholate or lipid-formulation amphotericin B are alternatives, as is caspofungin and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole.
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	• Fluconazole is the drug of choice for the prophylaxis of invasive candidiasis before engraftment in allogeneic HCT recipients, and may be started from the beginning or just after the end of the conditioning regimen. • The optimal duration of fluconazole prophylaxis is not defined. • Fluconazole is not effective against *C krusei* and *C glabrata* and should not be used for prophylaxis against these strains. • Micafungin is an alternative prophylactic agent. • Itraconazole oral solution has been shown to prevent invasive fungal infections, but use of this drug is limited by poor tolerability and toxicities. • Voriconazole and posaconazole may be used for prevention of

Clinical Guideline	Recommendation(s)
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**[52] **(2009)**	candidiasis post-engraftment. • Oral amphotericin B, nystatin, and clotrimazole troches may control superficial infection and control local candidiasis but have not been shown to prevent invasive candidiasis. • Transplant patients with candidemia or candidiasis may still receive transplants if their infection is diagnosed early and treated aggressively with amphotericin B or appropriate doses of fluconazole. • Autologous recipients have a lower risk of infection compared to allogeneic recipients and may not require prophylaxis, though it is still recommended in patients who have underlying hematologic malignancies, those who will have prolonged neutropenia and mucosal damage, or have recently received fludarabine. Itraconazole oral solution has been shown to prevent mold infections. • In patients with GVHD, posaconazole has been reported to prevent invasive mold infections. • Patients with prior invasive aspergillosis should receive secondary prophylaxis with a mold-active drug. The optimal drug has not been determined, but voriconazole has been shown to have benefit for this indication.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the echinocandins 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 Echinocandins[1-6]

Indication	Anidulafungin	Caspofungin	Micafungin
Candidemia and other forms of *Candida* infections (intra-abdominal abscesses and peritonitis)	✔		
Candidemia and other forms of *Candida* infections (intra-abdominal abscesses, peritonitis, and pleural space infections)		✔	
Candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses			✔
Esophageal candidiasis	✔	✔	✔
Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation			✔
Empirical therapy for presumed fungal infections in febrile, neutropenic patients		✔	
Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (e.g., amphotericin B, lipid formulations of amphotericin B, itraconazole)		✔	

IV. Pharmacokinetics

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

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

Generic Name(s)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Anidulafungin	>99	Chemical degradation	Renal (<1) Feces (30)	26.5
Caspofungin	97	Liver	Renal (41) Feces (35)	8-13
Micafungin	99	Liver	Renal (<15) Feces (70)	5-17

V. Drug Interactions

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

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

Generic Name(s)	Significance Level	Interaction	Mechanism
Caspofungin, micafungin	2	Cyclosporine	The pharmacologic effects of caspofungin may be increased by cyclosporine. Transient increases of liver function tests up to 3 times normal may occur when caspofungin and cyclosporine are taken concomitantly.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the echinocandins are listed in Table 7.

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

Adverse Events	Anidulafungin	Caspofungin	Micafungin
Cardiovascular System			
Arrhythmia	-	<5	<1
Atrial fibrillation	<2	<5	3-5
Bradycardia	-	<5	3-5
Bundle branch block (right)	<2	-	-
Cardiac arrest	-	<5	<1
Cyanosis	-	-	<1
ECG abnormality	<2	-	-
Edema	-	<5	5
Hypertension	<2	5-10	3-5
Hypotension	<2	3-20	6-10
Myocardial infarction	-	<5	<1
Peripheral edema	<2	6-11	7
QT prolongation	<2	-	-
Shock	-	-	<1
Sinus arrhythmia	<2	-	-
Tachycardia	-	4-11	3-8

Adverse Events	Anidulafungin	Caspofungin	Micafungin
Ventricular extrasystoles	<2	-	-
Central Nervous System			
Anxiety	-	<5	6
Chills	-	9-23	-
Confusion	-	<5	-
Delirium	-	-	<1
Depression	-	<5	-
Dizziness	<2	<5	-
Encephalopathy	-	-	<1
Fatigue	-	<5	6
Fever	<2	6-30	7-20
Headache	<2	5-15	2-16
Insomnia	-	<5	4-10
Intracranial hemorrhage	-	-	<1
Seizure	<2	<5	<1
Somnolence	-	<5	-
Tremor	-	<5	-
Dermatological			
Erythema	<2	4-9	-
Erythema multiforme	-	<5	<1
Flushing	<2	<5	-
Petechiae	-	<5	-
Pruritus	<2	6-7	6
Rash	<2	4-23	2-9
Skin exfoliation	-	<5	-
Skin lesion	-	<5	-
Skin necrosis	-	-	<1
Stevens-Johnson syndrome	-	<5	<1
Toxic epidermal necrolysis	-	-	<1
Urticaria	<2	<5	<1
Endocrine and metabolic			
Acidosis	-	-	<1
Cholestasis	<2	-	-
Hot flushes	<2	-	-
Jaundice	-	<5	-
Gastrointestinal			
Abdominal distension	-	<5	-
Abdominal pain	<2	4-9	2-10
Anorexia	-	<5	6
Appetite decreased	-	<5	-
Constipation	<2	<5	11
Diarrhea	3	6-27	8-23
Dyspepsia	-	-	6
Dyspepsia	<2	-	-
Fecal incontinence	<2	-	-
Hiccups	-	-	<1
Mucosal inflammation	-	4-10	14
Nausea	<2	4-15	7-22
Pancreatitis	-	<5	-
Vomiting	<2	6-17	7-22
Genitourinary			
Anuria	-	-	<1
Hematuria	-	10	-
Hemoglobinuria	-	-	<1

Adverse Events	Anidulafungin	Caspofungin	Micafungin
Nephrotoxicity	-	<5	-
Oliguria	-	-	<1
Renal failure/insufficiency	-	<5	<1
Renal tubular necrosis	-	-	<1
Urinary tract infection	-	<5	-
Hematological			
Anemia	-	2-11	3-10
Coagulopathy	<2	-	<1
Febrile neutropenia	-	-	6
Hematocrit decreased	-	13-18	-
Hemoglobin decreased	-	18-21	-
Hemolysis	-	-	<1
Hemolytic anemia	-	-	<1
Leukopenia	<1	-	-
Neutropenia	1	-	14
Pancytopenia	-	-	<1
Thrombocytopenia	<2	<5	4-15
Thrombotic thrombocytopenia purpura	-	-	<1
White blood cell decreases	-	12	<1
Hepatic			
Hepatic dysfunction	<2	-	<1
Hepatic failure	-	<5	<1
Hepatic necrosis	<2	<5	-
Hepatitis	<2	-	-
Hepatocellular damage	-	-	<1
Hepatomegaly	-	<5	<1
Hepatotoxicity	-	<5	-
Jaundice	-	-	<1
Laboratory Test Abnormalities			
Albumin decreased	-	7	-
Alkaline phosphatase increased	<2	9-22	6-8
ALT increased	-	-	5
Amylase increased	<2	-	-
AST increased	-	-	6
Bilirubin increased	<2	5-13	-
BUN increased	-	4-9	<1
CPK increased	<2	-	-
GGT increased	<2	-	-
Hyperbilirubinemia	-	-	<1
Hypercalcemia	<2	<5	-
Hyperglycemia	<2	6	6
Hyperkalemia	<2	<5	4-5
Hypernatremia	<2	-	4-6
Hypocalcemia	-	-	7
Hypoglycemia	-	-	6-7
Hypokalemia	3	5-23	14-18
Hypomagnesemia	<2	7	6-13
Hyponatremia	-	-	<1
Lipase increased	<2	-	-
Platelet count increased	<2	-	-
Prothrombin time prolonged	<2	-	-
Serum creatinine increased	<2	3-11	<1
Transaminases increased	<1 to 2	2-18	-
Urea increased	<2	-	-

Adverse Events	Anidulafungin	Caspofungin	Micafungin
Musculoskeletal			
Arthralgia	-	<5	<1
Back pain	<2	<5	5
Rigors	<2	-	9
Weakness	-	<5	-
Respiratory			
Apnea	-	-	<1
Cough	<2	6-11	8
Dyspnea	-	9	6
Epistaxis	-	<5	6
Hypoxia	-	<5	<1
Pleural effusion	-	9	-
Pneumonia	-	4-11	<1
Pulmonary edema	-	<5	-
Pulmonary embolism	-	-	<1
Rales	-	7	-
Respiratory distress	-	≤8	-
Stridor	-	<5	-
Tachypnea	-	<5	-
Other			
Anaphylaxis	-	<5	-
Angioneurotic edema	<2	-	-
Bacteremia	-	<5	5-9
Blurred vision	<2	-	-
Candidiasis	<2	-	-
Clostridial infection	<2	-	-
Coagulopathy	-	<5	-
Deep vein thrombosis	<2	-	<1
Disseminated intravascular coagulation	-	-	<1
Dystonia	-	<5	-
Eye pain	<2	-	-
Facial edema	-	-	<1
Febrile neutropenia	-	<5	-
Fluid overload	-	<5	5
Fungemia	<2	-	-
Infection	-	1-9	<1
Infusion-related reaction	<2	20-35	-
Injection site necrosis	-	-	<1
Injection site thrombosis	-	-	<1
Pain (extremities)	-	<5	-
Phlebitis	<2	18	5-19
Sepsis	-	5-7	5-6
Septic shock	-	11-14	-
Sweating	<2	-	-
Thrombophlebitis	<2	18	<1
Vasodilation	-	-	<1
Visual disturbance	<2	-	-

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

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

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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Anidulafungin	Candidemia and other *Candida* Infections: 200 mg loading dose on day 1, followed by 100 mg daily thereafter. Treatment should continue for at least 14 days after the last positive culture. Esophageal Candidiasis: 100 mg loading dose on day 1, followed by 50 mg daily thereafter. Patients should be treated for a minimum of 14 days and at least 7 days following resolution of symptoms.	Safety and efficacy in children have not been established.	Injection: 50 mg 100 mg
Caspofungin	Candidemia and other *Candida* Infections: 70 mg loading dose on day 1, followed by 50 mg daily thereafter. Treatment should continue for at least 14 days after the last positive culture. Empirical Therapy: 70 mg loading dose on day 1, followed by 50 mg daily thereafter. Empirical therapy should be continued until resolution of neutropenia. Patients found to have a fungal infection should be treated for at least 14 days; treatment should continue for at least 7 days after resolution of neutropenia and clinical symptoms. Esophageal Candidiasis: 50 mg daily for 7 to 14 days after symptom resolution Invasive Aspergillosis: 70 mg loading dose on day 1, followed by 50 mg daily thereafter. Total duration of therapy depends on severity of underlying disease, recovery from immunosuppression, and clinical response.	Unspecified Infections: 3 months to 17 years of age: 70 mg/m^2 loading dose on day 1, followed by 50 mg/m^2 daily thereafter. The maximum loading dose and the daily maintenance dose should not exceed 70 mg, regardless of the patient's calculated dose.	Injection: 50 mg 70 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Micafungin	Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses: 100 mg once daily Esophageal Candidiasis: 150 mg once daily Prophylaxis of *Candida* Infections in Hematopoietic Stem Cell Transplant Recipients: 50 mg once daily	Safety and efficacy in children have not been established.	Injection: 50 mg 100 mg

VIII. Effectiveness

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

Table 9. Comparative Clinical Trials with the Echinocandins

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aspergillosis				
Kartsonis et al.[10] (2005) Caspofungin 70 mg loading dose, followed by 50 mg daily for 28-90 days	OL Patients 18-80 years of age with definite or probable invasive aspergillosis who were refractory or intolerant to amphotericin B or a lipid preparation of amphotericin B	N=48 14 days posttreatment follow-up	Primary: Clinical response (favorable= complete or partial response; complete= resolution of signs, symptoms, radiographic findings, and bronchoscopic findings; partial= clinically meaningful improvement in above criteria)	Primary: A favorable response was seen in 44% of patients treated with caspofungin. A complete response was seen in 20% of patients treated with caspofungin. A partial response was seen in 24% of patients treated with caspofungin.
Maertens et al.[11] (2004) Caspofungin 70 mg loading dose, followed by 50 mg daily for an average of 28 days	OL, MC Patients with proven or probable invasive aspergillosis who were refractory or intolerant to amphotericin B, lipid formulations of amphotericin B, and itraconazole	N=83 28 day posttreatment follow-up	Primary: Clinical response (favorable= complete or partial response; complete response= resolution of all signs, symptoms, radiologic and/or bronchoscopic evidence; partial response= clinically meaningful improvement in the	Primary: Favorable response was seen in 44.6% of patients treated with caspofungin. Relapse was observed in 9.7% of patients, though only 1 case was confirmed microbiologically. Significantly more patients with hematological malignancies had a favorable response compared to patients who had undergone allogeneic hematopoietic stem cell transplant (P<0.01). Significantly more patients who were intolerant to standard therapy (amphotericin B formulations, itraconazole) had a favorable response compared to patients who were refractory to standard therapy (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			above measures) Secondary: Eradication	Secondary: Eradication or presumptive eradication was observed in 33.8% of patients. Eradication was observed in 28% of patients infected with *Aspergillus fumigatus*, 54% infected with *A flavus*, and 25% infected with *A niger*.
Maertens et al.[12] (2006) Caspofungin 70 mg daily in combination with either an azole (itraconazole or voriconazole) or a polyene (amphotericin B deoxycholate or an amphotericin B lipid preparation) All patients received active treatment with combination therapy.	OL, MC Patients 16 years of age and older with definite or probable invasive aspergillosis who were refractory or intolerant to standard antifungal therapy	N=53 12 months posttreatment follow-up	Primary: Clinical response (favorable= complete or partial response; complete response= resolution of all signs, symptoms, radiologic and/or bronchoscopic evidence; partial response= clinically meaningful improvement in the above measures)	Primary: At the end of combination therapy, 55% of patients had a favorable response. Of the patients with a favorable response (29), 4 showed a complete response and 25 showed a partial response. At day 84, 49% of patients had a favorable response. Success at the end of combination therapy ranged from 43% in the caspofungin plus itraconazole group to 60% in the caspofungin plus voriconazole group. In the caspofungin plus polyene group, success rates were 80%, 29%, and 50% for amphotericin B deoxycholate, amphotericin B lipid complex, and liposomal amphotericin B, respectively. Of 46 refractory patients, the addition of caspofungin to the initially refractory antifungal agent demonstrated a favorable response in 66% of patients. Success was observed in 20% of patients who were initially refractory to caspofungin and had a non-echinocandin antifungal agent added. Of the patients who were refractory to voriconazole therapy, 73% had a favorable response when caspofungin was added to voriconazole compared to a 40% favorable response rate in patients who discontinued voriconazole and switched to 2 new antifungal agents.
Caillot et al.[34] (2007) Caspofungin 70	RCT, MC Immuno-compromised	N=30 12 week posttreatment	Primary: Percentage of patients who had favorable overall	Primary: The overall response at EOT was significantly more favorable for patients in the combination group (67%) compared with patients in the high-dose monotherapy group (27%; P=0.028).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg on day 1, followed by 50 mg daily thereafter plus liposomal amphotericin B 3 mg/kg per day vs liposomal amphotericin B 10 mg/kg per day	patients ≥10 years of age with proven or probable invasive aspergillosis	follow-up	responses (partial or complete responses) at the end of therapy (EOT). Secondary: Time to favorable overall response, time to complete response, survival at EOT, percentage of patients with recurrent infection (defined as failure for overall response), and survival during the 4-week posttreatment follow-up	Secondary: At week 12, a favorable response was obtained by 10 of 15 patients in the high-dose monotherapy group (67%; 8 patients had a partial response and 2 patients had a complete response) and by 12 of 15 patients in the combination group (80%; 9 patients had a partial response and 3 patients had a complete response). A favorable or unfavorable response at EOT was independent of hematologic status at EOT (recurrence, remission, or stable; P=0.442). The survival rate at EOT was 97% (1 death had occurred in the high-dose monotherapy group). At week 12, all 15 patients in the combination group were alive, whereas 3 of 15 patients had died in the high-dose monotherapy group. Those 3 patients died due to progression of the underlying hematologic condition; and, in 1 patient, fungal infection contributed to the death. Study drug-related adverse events were less frequent in the combination group than in the high-dose monotherapy group.
Kontoyiannis et al.[40] (2009) Micafungin 75 mg/day IV daily (1.5 mg/kg/day for patients <40 kg) alone or in addition to the patient's current systemic antifungal regimen for up to 90 days	OL Adult and pediatric hematopoietic stem cell transplant (HSCT) patients with proven or probable invasive aspergillosis (IA)	N=98 2-425 days	Primary: Global response to treatment, based on clinical, radiological, and mycological assessment at the end of therapy	Primary: The overall response rate was 26%. An additional 12 patients had stable infections. A response to treatment was seen in 22% of the patients in the *de novo* treatment group, 24% in the refractory IA group, 100% in the toxicity failure group, 24% in the combination therapy group, and 38% in the micafungin-alone group. There were no significant differences in response according to the type of transplant, site of infection, or infecting *Aspergillus* species. Adverse events that occurred in >2% of patients included nausea, increased alanine aminotransferase, vomiting, hyperbilirubinemia, and arthralgia.
Candidiasis (Mucosal)				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Krause et al.[19] (2004) Anidulafungin 100 mg loading dose on day 1, then 50 mg daily for 14-21 days vs fluconazole 200 mg oral loading dose, then 100 mg orally daily for 14-21 days	RCT, DB, PC, MC Patients 18-65 years of age with esophageal candidiasis and a predisposing risk factor for fungal infection	N=601 Up to 35 weeks	Primary: Endoscopic response at the end of therapy (cure=complete resolution of lesions, improvement= decrease of ≥1 grade from baseline) Secondary: Clinical response (absence or improvement in symptoms), myco-logical response (eradication)	Primary: Endoscopic success was observed in 97.2% of patients in the anidulafungin group and 98.8% of patients in the fluconazole group. No significant difference was observed. Secondary: Clinical success was observed in 97.2% of patients in the anidulafungin group and in 98% in the fluconazole group. No significant difference was observed. Mycological success was observed in 86.7% of patients in the anidulafungin group and in 90.9% in the fluconazole group.
Kartsonis et al.[20] (2004) Caspofungin 50 mg daily (esophageal or oropharyngeal candidiasis) or 70 mg loading dose, then 50 mg daily (invasive candidiasis)	OL Patients 18-80 years of age with mucosal or invasive candidiasis who were intolerant or refractory to amphotericin B therapy	N=37 7-14 days after last positive culture	Primary: Clinical response	Primary: Favorable outcomes were observed in 86% of patients who had mucosal candidiasis. Favorable outcomes were observed in 87% of patients with invasive candidiasis. Ten of 11 patients with previously failed fluconazole therapy responded to caspofungin. Thirteen of 14 patients who were refractory to multiple antifungals responded favorably to caspofungin. Eighty-three percent of patients with invasive disease who failed multiple antifungals responded favorably.
Arathoon et al.[21] (2002)	RCT, DB, DR Patients 18-65 years	N=140 10-18 days	Primary: Clinical response	Primary: A higher portion of patients in the caspofungin groups achieved a favorable clinical response (74% to 91%) compared to the amphotericin B

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Caspofungin 35 to 70 mg daily for 7-14 days vs amphotericin B 0.5 mg/kg/day for 7-14 days	of age with a diagnosis of oropharyngeal and/or esophageal candidiasis		Secondary: Microbiological eradication	treatment group (63%), however this was not statistically significant. More patients with oropharyngeal disease had a favorable response (85%) compared to those with esophageal involvement (73%). Secondary: Microbiological eradication was observed in a larger portion of patients in the caspofungin groups compared to the amphotericin B group. There was no significant difference in the clearance of *C albicans* versus non-*albicans* species.
Villanueva et al.[22] (2001) Caspofungin 50 mg for 14 days vs caspofungin 70 mg for 14 days vs amphotericin B 0.5 mg/kg/day for 14 days	RCT, DB, MC Patients 21-65 years of age with endoscopically and microbiologically documented *Candida* esophagitis	N=128 28 days	Primary: Combined clinical and endoscopic response and microbiological response	Primary: The highest response rate was observed in the caspofungin 70 mg group and the lowest was observed in the amphotericin B group. The mean differences in response rates for caspofungin versus amphotericin B were 11% (95% CI, -9% to 32%) and 26% (95% CI, 4%–50%) for those receiving 50 and 70 mg, respectively, at the primary end point 2 weeks after discontinuation of therapy. Analysis of all evaluable patients (per protocol) were similar to the modified intention-to-treat analysis for combined response rates: 88%, 96%, and 78% at the end of therapy and 77%, 89%, and 68% 2 weeks after discontinuation of therapy for patients receiving caspofungin 50 mg, caspofungin 70 mg and amphotericin B, respectively. Time to resolution of symptoms was not different for any of the treatment groups. More than half the patients in each treatment arm had resolution of all symptoms by day 4 of therapy. Symptoms persisted in 7%, 0%, and 13% of patients at the end of therapy in the groups receiving caspofungin 50 mg, caspofungin 70 mg and amphotericin B, respectively. Endoscopic improvement was slightly higher in the caspofungin groups compared to the amphotericin B groups. Marked reduction in endoscopic grade was observed in 74%, 89%, and 63% of patients in the caspofungin 50 mg group, 70 mg group and amphotericin B group, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Caspofungin had slightly higher fungal eradication rates compared to amphotericin B. *C albicans* was not isolated from 71%, 85%, and 60% of patients taking caspofungin 50 mg, 70 mg, and amphotericin B, respectively. Eradication rates for non-*albicans* species were 64%, 71%, and 40% for caspofungin 50 mg, 70 mg, and amphotericin B, respectively.
Villanueva et al.[23] (2002) Caspofungin 50 mg daily for 7 to 21 days vs fluconazole 200 mg daily for 7 to 21 days	RCT, DB, MC Patients with symptomatic, endoscopically and microbiologically documented *Candida* esophagitis	N=177 5-7 day posttreatment follow-up	Primary: Combined clinical and endoscopic response and microbiological response	Primary: Combined response rates in patients receiving caspofungin and fluconazole were 81% and 85%, respectively. No significant difference was seen between the treatment groups. Microbiological response was observed in 59% of patients in the caspofungin group and 76% of patients in the fluconazole group.
Kartsonis et al.[24] (2002) Caspofungin 35 mg, 50 mg, or 70 mg daily vs amphotericin B 0.5 mg/kg/day vs fluconazole 200 mg IV daily	RETRO Symptomatic patients with endoscopically confirmed *Candida* esophagitis and decreased susceptibility to fluconazole	N=32 3-14 days posttreatment follow-up	Primary: Clinical outcomes	Primary: Favorable response was seen in 64% of patients with infections which were clinically refractory to fluconazole and subsequently treated with caspofungin. Favorable response to caspofungin was seen in 79% of patients with infections that had decreased susceptibility to fluconazole.
Pettengell et al.[25]	MC, OL	N=120	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2004) Micafungin 12.5 to 100 mg daily for up to 14-21 days	Patients 18 years of age and older with human immunodeficiency virus (HIV) infection and endoscopically confirmed esophageal candidiasis	2-week posttreatment follow-up	Investigators' evaluation of clinical response at the end of therapy (success= cure or improvement in signs and symptoms) Secondary: Improvement in esophageal lesions	A positive clinical response was observed in all patients in all dose categories except for the 12.5-mg dose group, where all but 1 patient had a positive clinical response. A statistically significant dose-response relationship was observed in the proportion of patients cleared in each group: 33.3%, 53.8%, 86.7%, 84.2%, and 94.7% for the 12.5 mg, 25 mg, 50 mg, 75 mg, and 100 mg groups, respectively (P<0.001). Secondary: Based on endoscopy, the 75 mg and 100 mg doses were more effective in reducing mucosal lesions compared with the lower dose groups (P<0.001).
de Wet et al.[26] (2005) Micafungin 150 mg daily for up to 42 days vs fluconazole 200 mg IV for up to 42 days	RCT, DB, MC, PG Patients 16 years of age and older with endoscopically confirmed esophageal candidiasis (EC)	N=523 4-week posttreatment follow-up	Primary: Treatment success at the end of therapy Secondary: Clinical and mucosal response at the end of therapy, therapeutic response at the end of therapy, relapse at 2 and 4 weeks posttreatment	Primary: Endoscopic cure rate was 87.7% at the end of therapy in the micafungin group compared to 88.0% for fluconazole patients and no significant differences were observed. Secondary: The clinical success rates (cleared or improved) for micafungin and fluconazole were 94.2% and 94.6%, respectively. Overall therapeutic success rates for micafungin and fluconazole were 87.3% and 87.2%, respectively. The overall incidence of relapse at 2 and 4 weeks posttherapy was 15.2% and 11.3% in the micafungin and fluconazole groups, respectively (P>0.313).
de Wet et al.[27] (2004) Micafungin 50 mg, to 150 mg daily for up to 14-21 days vs fluconazole 200	RCT, DB, MC, PG Patients 18 years of age or older with HIV infection and endoscopically confirmed esophageal candidiasis (EC)	N=245 2-week posttreatment follow-up	Primary: Endoscopic cure rate and eradication rates Secondary: Change in endoscopic cure rate compared with baseline at day 14,	Primary: Comparisons of micafungin groups showed a dose-response relationship for endoscopic cure. Cure rates were 68.8%, 77.4%, and 89.9% for the 50-mg, 100 mg, and 150 mg dose groups, respectively (P=0.024 for comparison between the 3 groups; P=0.007 for the comparison of the 50 mg and 150 mg groups). There was no significant difference seen between the fluconazole group and either the 100 mg or 150 mg micafungin groups (P=0.136 and P=0.606, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg IV daily for up to 14-21 days			clinical response at end of treatment, EC severity score, overall therapeutic success, incidence of relapse	Fluconazole had a lower endoscopic cure rate than micafungin 150 mg in patients with an endoscopic grade 3 at baseline (77.8% and 100% respectively). Eradication rates were 35.1%, 78.3%, 57.1%, and 67.3% for the micafungin 50 mg, 100 mg, and 150 mg groups and the fluconazole group, respectively. Eradication rates for micafungin 100 mg were higher than for micafungin 150 mg (P=0.031). No significant difference was observed between micafungin 100 mg and fluconazole or micafungin 150 mg and fluconazole (P=0.263 and P=0.312, respectively). Secondary: All treatment groups showed an improvement in endoscopic findings at the end of treatment compared to baseline (P=0.003 for the micafungin groups). Endoscopic cure rate at day 14 and clinical response at the end of treatment were dose-dependent in the micafungin groups, and comparable in the 100 mg and 150 mg micafungin group and the fluconazole group (P=0.574). Therapeutic success was comparable between the 100 mg and 150 mg micafungin groups and the fluconazole group (P=0.463). The rates of improvement in EC severity scores were comparable in the 100 mg and 150 mg micafungin groups and the fluconazole group. Worsening EC severity or use of non-prophylactic antifungal therapy was observed in 9 patients in the micafungin group during follow-up and in no patients in the fluconazole group.
Candidiasis (Systemic)				
Pfaller et al.[13] (2005)	OL, DR Patients 18 years of	N=68 2-week	Primary: Clinical response (eradication of	Primary: Eradication rates were 74%, 85%, and 89% for the 50 mg, 75 mg, and 100 mg groups, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Anidulafungin 50 to 100 mg IV daily	age and older with candidemia and/or candidiasis	posttreatment follow-up	pathogen)	
Krause et al.[14] (2004) Anidulafungin 50 mg, 75 mg, or 100 mg IV daily	DR, OL Patients 18 years of age and older with invasive candidiasis and an expected survival of >72 hours	N=116 2-week posttreatment follow-up	Primary: Global response at the follow-up visit defined as both and microbiological response Secondary: Global response at end of treatment, clinical and micro-biological response at end of treatment and follow-up	Primary: Global response rates at follow-up were 72%, 85%, and 83% for the 50 mg, 75 mg, and 100 mg groups, respectively. Secondary: Global response rates at the end of treatment were 84%, 90%, and 89% for the 50 mg, 75 mg, and 100 mg groups, respectively. Microbiological response rates at the end of treatment were 84%, 93%, and 89% for the 50 mg, 75 mg, and 100 mg groups, respectively. Clinical response rates at the end of treatment were 88%, 90%, and 89% for the 50 mg, 75 mg, and 100 mg groups, respectively. Microbiological response rates at the follow-up visit were 78%, 85%, and 88% for the 50 mg, 75 mg, and 100 mg groups, respectively. Clinical response rates at the follow-up visit were 72%, 85%, and 83% for the 50 mg, 75 mg, and 100 mg groups, respectively
Reboli et al.[15] (2007) Anidulafungin 200 mg IV on day 1, then 100 mg daily for 14-42 days vs fluconazole 800 mg IV on day 1 then 400 mg daily for 14-42 days	RCT, DB, MC Patients ≥16 years of age with candidemia or other forms of invasive candidiasis	N=261 6-week posttreatment follow-up	Primary: Global response at the end of IV therapy (success= resolution of signs and symptoms and no need for additional antifungal therapy and eradication of *Candida* species) Secondary: Global response at the end of all	Primary: Significantly more patients in the anidulafungin group achieved a successful global response compared to the fluconazole group (75.6% and 60.2% respectively; P=0.01). Secondary: Significantly more patients in the anidulafungin group had a successful global response at the end of all therapy compared to the fluconazole group (74% and 56.8% respectively; P<0.02). Significantly more patients in the anidulafungin group had a successful global response at the 2-week follow-up compared to the fluconazole group (64.6% and 49.2% respectively; P<0.02). There was no significant difference in the proportion of patients in either

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients could receive oral fluconazole after 10 days of IV therapy.			therapy and at 2 and 6 weeks follow-up, per-patient and per-pathogen microbiological response at all time points, death from all causes	group who had a successful global response at the 6-week follow-up (55.9% and 44.1%, respectively). Microbiological success was observed for 88.1% of all pathogens in the anidulafungin group compared to 76.2% in the fluconazole group (P=0.02). There was no significant difference in all-cause mortality between the two treatment groups (P=0.13).
Reboli et al.[49] (2011) Anidulafungin 200 mg IV on day 1, then 100 mg daily for 14-42 days vs fluconazole 800 mg IV on day 1 then 400 mg daily for 14-42 days All patients could receive oral fluconazole after 10 days of IV therapy.	RCT, DB, MC (Post-hoc analysis) Patients ≥16 years of age with candidemia or other forms of invasive candidiasis. The study database was reviewed to identify all patients with systemic candidiasis caused by *C. albicans* only. Patients with nonalbicans *Candida* infections and mixed infections (*C. albicans* and another concurrent pathogen) at baseline were excluded.	N=261 6-week posttreatment follow-up	Primary: Global response at the end of IV therapy Secondary: Global response at the end of all therapy and at 2 and 6 weeks follow-up, microbiological response, death	Primary: The investigator-assessed global response rate at end of IV study treatment was higher in patients with *C. albicans* infections treated with anidulafungin compared to fluconazole: 81.1% versus 62.3% (95% CI, 3.7-33.9; P=0.02). Secondary: Significantly more patients in the anidulafungin group had a successful global response at the end of all therapy and 2-week follow-up compared to the fluconazole group. The time to negative blood culture was significantly shorter for anidulafungin compared with fluconazole (P<0.05); median times to negative blood culture were 2 and 5 days, respectively. Persistent infection was reported in 2.7% of patients in the anidulafungin group compared with 13.1% of patients in the fluconazole group (P<0.05). The proportion of patients who died during the 6-week period from study entry was 20.3% in the anidulafungin arm and 21.3% in the fluconazole arm (P=0.842). Fewer deaths occurred within 24 hours of end of treatment with anidulafungin than with fluconazole (4 vs 13; P=0.01). Both study drugs were well tolerated and the respective safety profiles in patients with *C. albicans* infection only were similar to those in the overall study populations.
Mora-Duarte et al.[16]	RCT, DB, DD	N=239	Primary: Overall response to	Primary: At the end of IV therapy, favorable response was observed in 73.4% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Caspofungin 70 mg loading dose followed by 50 mg daily thereafter vs amphotericin B 0.6-0.7 mg/kg/day (non-neutropenic patients) or 0.7-1.0 mg/kg/day (neutropenic patients) After 10 days of IV therapy, non-neutropenic patients could be switched to oral fluconazole 400 mg daily.	Patients 18 years of age and older with one or more positive *Candida* cultures in the previous 4 days	8-week posttreatment follow-up	treatment (favorable= resolution of signs and symptoms of infection and negative culture) at the end of IV therapy	patients in the caspofungin group and 61.7% in the amphotericin B group. After adjusting for neutropenic status, the difference in percentage with a favorable response was 12.7% (P=0.09). Among patients meeting the prespecified criteria for evaluation, 80.7% of caspofungin patients and 64.9% of amphotericin B patients had a favorable response (P=0.03). A larger portion of patients in the amphotericin B group had toxicities requiring a change in therapy compared to the caspofungin group (P=0.03).
DiNubile et al.[17] (2005) Caspofungin 70 mg loading dose followed by 50 mg daily thereafter vs amphotericin B 0.6-1.0 mg/kg/day	RETRO Adult patients with proven invasive candidiasis	N=239 14 days following last positive culture	Primary: Clinical outcome (favorable= complete resolution of signs and symptoms of disease and negative cultures)	Primary: Favorable responses were slightly lower in patients with cancer compared to those without cancer (62% and 70%, respectively). Favorable responses were seen in 61% of caspofungin patients and 50% of amphotericin B patients with hematological malignancies, and in 80% and 59%, respectively, in patients with solid organ malignancies. Of patients who were neutropenic at baseline, 46% responded favorably to treatment compared to 70% of non-neutropenic patients. Of neutropenic patients, 50% in the caspofungin group responded favorably compared to 40% in the amphotericin B group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients could be switched to oral fluconazole therapy after 10 days of IV therapy.				The response rate for non-*albicans Candida* species was 76% compared to 48% for *albicans* species. Favorable response rates for *C albicans* and *C tropicalis* infections were 56% and 71%, respectively, in the caspofungin group and 45% and 43%, respectively, in the amphotericin B group.
Betts et al.[30] (2009) Caspofungin 70 mg loading dose followed by 50 mg daily thereafter vs caspofungin 150 mg daily After ≥10 days of caspofungin therapy, patients either continued to receive caspofungin therapy or were switched to oral fluconazole.	RCT, MC, DB Adult patients ≥18 years of age with both clinical and microbiological evidence of invasive candidiasis at a sterile site	N=204 8-week posttreatment follow-up	Primary: Proportion of patients who developed a significant drug-related adverse event Secondary: Overall response (clinical and microbiological) at the end of therapy	Primary: Significant drug-related adverse events were reported for 2 patients (1.9%) in the 70/50 mg treatment group and 3 patients (3.0%) in the 150 mg treatment group (95% CI, -4.1 to 6.8). The incidences of drug-related clinical adverse events (13.5% vs 14.0%), serious drug-related clinical adverse events (0% vs 3.0%), and discontinuations of caspofungin therapy because of drug-related clinical adverse events (1.9% vs 2.0%) were similar between the 70/50 mg and 150 mg treatment groups, respectively. Secondary: At the end of caspofungin therapy, 71.6% of patients in the 70/50 mg treatment group and 77.9% of patients in the 150 mg treatment group had a favorable overall response. A favorable clinical response occurred for 71.6% of the 70/50 mg treatment group and 80.0% of patients in the 150-mg treatment group. A favorable microbiological response occurred for 82.4% of patients in the 70/50 mg treatment group and 88.4% of patients in the 150 mg treatment group. For each response category, there were no statistically significant differences between the treatment groups.
Pappas et al.[35] (2007) Caspofungin 70 mg loading dose	RCT, DB Patients ≥18 years of age with candidemia or	N=595 6-week posttreatment follow-up	Primary: Treatment success (defined as clinical and mycological success at the end	Primary: A successful outcome at the end of treatment was achieved by 76.4% of patients in the micafungin 100 mg group, 71.4% of patients in the micafungin 150 mg group, and 72.3% of patients in the caspofungin group. Both micafungin 100 mg and micafungin 150 mg were non-inferior

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by 50 mg daily thereafter vs micafungin 100 mg daily vs micafungin 150 mg daily After ≥10 days of IV therapy, patients were allowed to be switched to oral fluconazole 400 mg daily	invasive candidiasis		of blinded intravenous therapy)	to the caspofungin (95% CI, -4.4% to 12.3% and 95% CI, -9.3% to 7.8%, respectively). The overall response rates for patients with *C. albicans* were similar to those for patients with non-*albicans Candida* species across treatment arms. For patients with baseline APACHE II scores of ≤20 and >20, treatment success at the end of blinded intravenous therapy was similar across treatment arms. Success at the end of therapy, based on management of intravascular catheters, did not vary significantly between treatment arms. However, in each arm, patients who underwent intravascular catheter removal or replacement more often achieved treatment success, compared with patients who did not undergo catheter removal. In aggregate, 77.9% of patients whose intravascular catheter was removed or replaced achieved treatment success, compared with 63.2% of patients whose catheter was not removed or replaced (P=0.001). Persistently positive culture results as a cause of treatment failure were seen more frequently in micafungin 150 mg group (11.6%) and the caspofungin group (9.6%), compared with the micafungin 100 mg group (5.8%). Five percent of patients who received caspofungin had a culture-confirmed relapsed infection, compared with 4.5% who received micafungin 100 mg and 2.9% who received micafungin 150 mg. A total of 29.6% of patients who received one of the study drugs died. More patients died in the micafungin 100 mg arm (29%) and the micafungin 150 mg arm (33.2%) than in the caspofungin arm (26.4%). No deaths were related to the study drugs.
Cornely et al.[37] (2007) Caspofungin 70	MC, OL Patients ≥18 years of age with proven	N=48 12-week posttreatment	Primary: Overall clinical and microbiological	Primary: In the MITT population, 39 patients (81%) had a favorable overall response at the end of caspofungin therapy. Among the nine patients with an unfavorable response, four had persistently positive *Candida* cultures

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg loading dose followed by 50 mg daily thereafter or 100 mg daily without the loading dose (in patients with endocarditis, meningitis and osteomyelitis/ septic arthritis) After ≥10 days of caspofungin therapy, patients either continued to receive caspofungin therapy or were switched to oral fluconazole.	invasive candidiasis	follow-up	response	and three patients had an indeterminate efficacy assessment. The remaining two patients with unfavorable responses had persistent signs/symptoms of endocarditis (despite negative follow-up cultures) or developed metastatic *Candida* lesions while on caspofungin. Among the 42 patients included in the EP population, 37 (88%) demonstrated a favorable overall response at the end of caspofungin therapy. Efficacy was also assessed at day 10 of caspofungin and at the end of all antifungal therapy. Seventy-nine percent (38/48) responded favorably at the end of all antifungal therapy. Sixty-nine percent (22/32) also had a successful outcome at the day 10 assessment. Eleven patients (23%) died while on caspofungin therapy or during the 12 week posttreatment period. None of the deaths was attributed to caspofungin. In five patients, mortality was directly attributed to the underlying *Candida* infection. The remaining deaths were the result of other co-morbidities. Among the 48 patients, 43 (90%) developed ≥1 adverse event.
DiNubile et al.[33] (2008) Caspofungin 70 mg loading dose, followed by 50 mg daily thereafter	RETRO <u>Invasive Candidiasis Protocol 014</u>: Patients ≥18 years old with clinically and microbiologically documented invasive candidiasis <u>Invasive Aspergillosis Protocol 019:</u> Patients ≥18 years	N=159 Variable duration	Primary: Clinical outcomes and safety	Primary: A favorable response to caspofungin was observed in more elderly than non-elderly patients with invasive candidiasis (83% vs 68%) or invasive aspergillosis (64% vs 44%). Fewer elderly than non-elderly patients with invasive candidiasis had a favorable response to amphotericin B (42% vs 70%). In the Empirical Therapy Study, an overall favorable response occurred in similar proportions of elderly and non-elderly patients in both treatment groups. Both treatment groups also had similar proportions of elderly and non-elderly patients with a favorable response on the individual outcome components, except that survival to 7 days posttreatment was lower in elderly patients versus non-elderly patients receiving liposomal amphotericin B (78% vs 91%). In all three studies, clinical and laboratory adverse events related to caspofungin occurred in similar proportions of elderly and non-elderly patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	old with definite or probable invasive aspergillosis refractory to or intolerant of amphotericin or itraconazole Empirical Therapy Protocol 026: Patients ≥16 years old with persistent fever and neutropenia after 96 hours of parenteral systemic antibacterial therapy			The all-cause mortality rate was higher in elderly patients versus non-elderly patients in both treatment groups in the Invasive Candidiasis Study and the Empirical Therapy Study, but was lower in elderly versus non-elderly patients in the Invasive Aspergillosis Study. Nephrotoxicity and systemic infusion-related events occurred in similar proportions of elderly and non-elderly patients in all treatment groups in all three studies. Infusion-site tolerability was also similar in elderly and non-elderly patients: caspofungin infusion was well-tolerated in over 95% of both age groups; amphotericin B infusion was well tolerated in 100% of elderly patients and 89% of non-elderly patients.
Queiroz-Telles et al.[41] (2008) Micafungin 2 mg/kg/day (≤40 kg) or 100 mg/day (>40 kg) vs liposomal amphotericin B 3 mg/kg/day	RCT, DB Pediatric patients <16 years old with clinical signs of systemic *Candida* infection and one or more positive *Candida* cultures from blood or another sterile site within the previous 4 days	N=106 12-week posttreatment follow-up	Primary: Response rate based on the assessment of overall treatment success (clinical and mycological response at the end of therapy)	Primary: In the modified intent-to-treat (MITT) population, the rate of overall treatment success was similar for micafungin (72.9%) compared with liposomal amphotericin B (76%; 95% CI, -20.1 to 15.3). Consistent findings were observed for the per protocol population, which showed success rates of 85.4% and 88.1% in the micafungin and liposomal amphotericin B groups, respectively (95% CI, -16.4 to 12.7). Mycologic persistence at the end of therapy was observed for 15.6% patients in both the micafungin and liposomal amphotericin B groups in the MITT population. Three patients in the micafungin group and none in the liposomal amphotericin B group had a proven recurrent fungal infection during the posttreatment phase. The mortality rate during the treatment phase was 1.9% for micafungin and 11.1% for liposomal amphotericin B in the ITT population. During the entire study, including the 12-week follow-up, the mortality rates were 25.0% and 24.1% of patients, respectively. The fungal infection was considered by the investigator to have contributed to the cause of death for 7.7% and 5.6% of patients, respectively.

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				The incidence of adverse events was similar between the treatment groups.
Kuse et al.[43] (2007) Micafungin 2 mg/kg/day (≤40 kg) or 100 mg/day (>40 kg) vs liposomal amphotericin B 3 mg/kg/day	RCT, DB Patients ≥16 years old with clinical signs of systemic *Candida* infection and one or more positive *Candida* cultures from blood or another sterile site within the previous 4 days	N=531 12-week posttreatment follow-up	Primary: Response rate based on the assessment of overall treatment success (clinical and mycological response at the end of therapy)	Primary: In the modified intention-to-treat population (MITT), 74.1% of patients were treated successfully with micafungin versus 69.6% of those treated with lipo somal amphotericin B (95% CI, –3.0 to 12.8). In the intention-to-treat population (ITT), success rates were 71.6% with micafungin and 68.2% with liposomal amphotericin B 95% CI, -3.9 to 11.6). In the per-protocol population, treatment success rates were 81.4% for micafungin and 80.4% for liposomal amphotericin B (95% CI, -6.1 to 9.6). Mycological persistence at the end of therapy was observed in 9% of patients in the micafungin group and 9% of patients in the liposomal amphotericin B group in the per-protocol population. Species specificity for mycological persistence was similar between treatment groups. A recurrent *Candida* infection during the 12-week posttreatment period was seen in 7 patients who had received micafungin and 6 patients who had received liposomal amphotericin B; the minimum inhibitory concentration (MIC) values showed no marked changes relative to the baseline MIC values for these patients. In the ITT population, 18% of patients died in the micafungin group and 17% of patients died in the liposomal amphotericin B group during the treatment phase. During the study, including the 12-week follow-up period, 40% of patients in the micafungin group and 40% of patients in the liposomal amphotericin B group died. The fungal infection was considered by the investigator to have contributed to the cause of death for 13% patients in the micafungin group and 9% patients in the liposomal amphotericin B group (P=0.22). There were fewer treatment-related adverse events in the micafungin group than in the liposomal amphotericin B group. There were fewer cases of hypokalemia, rigors, increased serum creatinine, and back pain in the micafungin group than in the liposomal amphotericin B group, as well as fewer infusion-related reactions.
Gafter-Gvili et	MA	N=3,265	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
al.[32] (2008) Group 1 Echinocandins vs other antifungal agents Group 2 Fluconazole vs other antifungal agents	Patients with confirmed invasive candidiasis	(15 trials) Variable duration	30-day all-cause mortality Secondary: Treatment failure, microbiological failure, adverse events	Fluconazole vs other antifungal agents (9 studies) No difference in mortality was observed with fluconazole vs amphotericin B (RR, 0.92; 95% CI, 0.72-1.17). No difference in mortality was observed between fluconazole and itraconazole (RR, 1.91; 95% CI, 0.39-9.35) or between fluconazole and a combination of fluconazole and amphotericin B (RR, 0.98; 95% CI, 0.70-1.35). Echinocandins vs other antifungal agents (4 studies) There was no difference in mortality with anidulafungin vs fluconazole (RR, 0.73; 95% CI, 0.48-1.10). There was no difference in mortality with caspofungin vs amphotericin B (RR, 1.08; 95% CI, 0.75-1.55) or with micafungin vs liposomal amphotericin B (RR, 1.04; 95% CI, 0.75-1.43). Other comparisons (2 studies) There was no difference in mortality with micafungin vs caspofungin (100 mg/d: RR, 1.10; 95% CI, 0.80-1.51; 150 mg/d: RR, 1.27; 95% CI, 0.93-1.72). There was no difference in mortality with amphotericin B plus fluconazole vs voriconazole (RR, 1.18; 95% CI, 0.90-1.54). Secondary: Fluconazole vs other antifungal agents (9 studies) No significant difference in treatment failure was found with fluconazole and amphotericin B (RR 1.22; 95% CI, 0.97-1.54) or with fluconazole vs a combination of fluconazole and amphotericin B (RR 1.41; 95% CI, 0.99-1.99). Microbiological failure was higher in patients treated with fluconazole compared to amphotericin B (RR 1.52; 95% CI, 1.12-2.07) or with fluconazole vs a combination of fluconazole and amphotericin B (RR 2.69; 95% CI, 1.17-6.18).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No difference in adverse events requiring discontinuation was noted with fluconazole vs amphotericin B (RR 0.45; 95% CI, 0.13-1.56), itraconazole (RR 0.32; 95% CI, 0.04-2.82) or with fluconazole vs a combination of fluconazole and amphotericin B (RR 1.16; 95% CI, 0.49-2.75). Fluconazole caused less nephrotoxicity than amphotericin B (RR, 0.11; 95% CI, 0.03-0.48) or the combination of amphotericin B and fluconazole (RR, 0.12; 95% CI, 0.04-0.39). <u>Echinocandins vs other antifungal agents (4 studies)</u> Treatment failure significantly decreased with anidulafungin vs fluconazole (RR, 0.61; 95% CI, 0.42-0.89). There was no difference in treatment failure with caspofungin vs amphotericin B (RR, 0.70; 95% CI, 0.47-1.03) or with micafungin vs liposomal amphotericin B (RR, 0.93; 95% CI, 0.74-1.19). Microbiological failure was significantly reduced with anidulafungin vs fluconazole (RR, 0.50; 95% CI, 0.29-0.86). No difference in microbiological failure was noted for caspofungin vs amphotericin B (RR, 0.95; 95% CI, 0.40-2.25) or with micafungin vs liposomal amphotericin B (RR, 1.01; 95% CI, 0.53-1.92). A significant decrease in adverse events requiring discontinuation was observed with anidulafungin vs fluconazole (RR, 0.52; 95% CI, 0.29-0.92). Caspofungin was associated with a significantly lower rate of adverse events requiring discontinuation when compared with amphotericin B (RR, 0.11; 95% CI, 0.04-0.36) or liposomal amphotericin B (RR, 0.45; 95% CI, 0.26-0.80). <u>Other comparisons (2 studies)</u> There was no difference in treatment failure with micafungin and caspofungin (100 mg/d: RR, 0.85; 95% CI, 0.60-1.20; 150 mg/d: RR, 1.04; 95% CI, 0.74-1.42). There was no difference in treatment failure with amphotericin B plus fluconazole vs voriconazole (RR, 1.00; 95% CI, 0.83-1.19). There was no difference in microbiological failure with micafungin and caspofungin (100 mg/d: RR, 0.73; 95% CI, 0.41-1.22; 150 mg/d: RR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				1.10; 95% CI, 0.70-1.73). There was no difference in adverse events requiring discontinuation with micafungin and caspofungin. Adverse events requiring discontinuation were significantly lower (RR, 0.47; 95% CI, 0.23-0.93) and nephrotoxicity was significantly higher (RR, 2.64; 95% CI, 1.57-4.44) with the amphotericin B-fluconazole arm compared to voriconazole.
Empirical Therapy				
Kubiak et al.[45] (2010) Caspofungin70 mg for 1 dose, then 50 mg daily vs micafungin 100 mg daily	RETRO, OBS Patients who had received ≥2 doses on concurrent days of either caspofungin or micafungin for the empirical treatment of febrile neutropenia (FN)	N=149 Variable duration	Primary: Treatment success, survival to hospital discharge, breakthrough invasive fungal disease (IFD) during therapy or within 7 days after completion of therapy, and discontinuation of therapy due to adverse events	Primary: Three IFDs were diagnosed at baseline in the caspofungin group and 6 in the micafungin cohort (2.0% vs 3.4%; P=NS). Treatment of baseline IFD was successful in 1.3% of patients receiving caspofungin and 2.3% of patients receiving micafungin. A total of 8.1% of patients in the caspofungin group and 7.5% of patients in the micafungin group died (RR, 0.93; 95% CI, 0.44–1.97; P=NS). The incidence of breakthrough IFD was similar between groups: 10.7% of patients receiving caspofungin and 12.1% of patients in the micafungin group (RR, 1.12; 95% CI, 0.61–2.07; P=NS). The probability of breakthrough IFD during echinocandin treatment at 7, 14, and 21 days of administration was 3%, 8%, and 14% when micafungin was used, and 6%, 10%, and 15% when caspofungin was used, respectively (P=NS for all time points). There were 3 adverse events related to caspofungin (2.0%) and there were 2 adverse events requiring discontinuation observed in patients receiving micafungin (1.1%). When the combination of successful treatment of baseline fungal infections, survival at hospital discharge, absence of breakthrough IFD, and no discontinuation of echinocandin treatment because of AEs was considered as a single outcome, a favorable response was observed in 81.9% of patients receiving caspofungin and in 81.0% of patients receiving micafungin (RR, 0.99; 95% CI, 0.89–1.10; P=NS).
Ellis et al.[18]	RETRO	N=73	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2006) Caspofungin 70 mg loading dose, then 50 mg daily for at least 10-14 days vs liposomal amphotericin B 3 mg/kg/day for neutropenic fever (NF) or 5 mg/kg/day for invasive pulmonary aspergillosis (IPA) for at least 10-14 days	Patients with acute hematological malignancies with prolonged neutropenia or invasive fungal infections	7 day posttreatment follow-up	All cause mortality within 7 days of completion of antifungal therapy, response to treatment, toxicity Secondary: All antifungal drug administration during each hospital admission	Significantly more deaths were seen in patients following caspofungin therapy compared to liposomal amphotericin B therapy (P=0.013). Overall, response to therapy did not differ significantly between treatment groups (P>0.16). Significantly more patients experienced treatment failure due to a breakthrough invasive fungal infection in the caspofungin group compared to the amphotericin B group (P=0.047). The proportion of events treated with amphotericin B which were associated with at least 1 adverse event was significantly higher compared to the caspofungin group (P=0.02). Significantly more patients in the amphotericin B group experienced episodes of hypokalemia (P=0.01). A similar proportion of drug discontinuations was observed due to adverse effects between the groups (P=0.48). Secondary: There were a total of 97 episodes of treatment with either caspofungin or liposomal amphotericin B and results were similar to those seen in the primary efficacy endpoints.
Maertens et al.[47] (2010) Caspofungin 70 mg/m^2 loading dose on day 1, then 50 mg/m^2 daily vs liposomal amphotericin B (L-AmB)	MC, DB, RCT Patients 2 to 17 years of age who had received chemotherapy for cancer or had undergone HSCT, had received parenteral broad-spectrum antibacterial therapy for ≥96 hours, and	N=83 Up to 28 days	Primary: Safety and tolerability Secondary: Efficacy	Primary: Serious clinical adverse events that were considered to be drug related were reported in 1 (1.8%) caspofungin recipient (hypotension) and 3 (11.5%) L-AmB recipients (hyperbilirubinemia; circumoral edema; and angioneurotic edema with dyspnea, laryngospasm, and tachycardia); all 4 patients discontinued the intended course of therapy. Three patients died during the study: 2 (3.6%) in the caspofungin group and I (3.8%) in the L-AmB group. Secondary: A favorable overall response was observed in 46.4% of patients who received caspofungin and 32.0% of those who received L-AmB; however,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
3 mg/kg daily	were neutropenic and febrile			the 95% CIs for the treatment groups overlapped.
Toubai et al.[29] (2007) Micafungin 50-300 mg IV daily for ≥5 days	OL Patients aged 27-82 years with febrile neutropenia for whom antibiotic therapy was not effective	N=23 5-43 days	Primary: Treatment success (based on clinical and mycological response at the end of therapy)	Primary: The overall treatment success rate was 73.9%. None of the patients developed breakthrough fungal infections, discontinued the drug due to lack of efficacy, or died during the study period. The treatment success rates by primary diagnosis were 77.8% in patients with AML, 50.0% in patients with NHL, and 87.5% in patients with other diseases. The treatment success rate in patients who had previously received antifungal prophylaxis was not significantly different from those who had not received prophylaxis. The treatment success rate for patients with mild neutropenia (501 -1000 cells/µl) was 100% (5 of 5 patients). Treatment success rate for patients with moderate neutropenia (101 - 500 cells/µl) and severe neutropenia (100 or less cells/µl) were both 66.7% (2 of 3 patients with moderate neutropenia and 10 of 15 patients with severe neutropenia). The treatment success rate in the severe neutropenia group and mild neutropenia group were not significantly different (P=0.266). The treatment success rate by maximum doses of micafungin were 0% in patients administered 50 mg and 75 mg (0/2 and 0/1, respectively), 100% in patients administered 100 mg (8/8), 70.0% in patients administered 150 mg (7/10) and 100% in patients administered 300 mg (2/2). Treatment was not discontinued because of an adverse event in any of the patients. One or more adverse events occurred in 21.7% of the patients during the study.
Park et al.[50] (2010) Micafungin 100 mg IV once daily for ≥5 days	PRO, MC Patients ≥18 years of age who were receiving chemotherapy for	N=47 Variable duration	Primary: Response to therapy (success=no breakthrough fungal infection,	Primary: A total of 29 patients responded to micafungin therapy according to the composite score (61.7%), 89.4% of the patients did not show a spiking fever within 7 days of the end of therapy, and 66% of the patients completed their micafungin treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	hematological diseases who had neutropenia and an unexplained high fever that was refractory to combined antimicrobial treatment for at least 72 hours		survival for 7 days post-therapy, did not discontinue therapy prematurely, resolution of fever, and successfully treated fro any baseline fungal infection)	About 77% of the patients experienced resolution of their fevers prior to their recovery from neutropenia. The median duration of neutropenia, fever and neutropenic fever was 6 days, 3 days, and 2 days, respectively. Grade 3 or 4 hyperbilirubinemia and AST elevation was observed in 6.4% and 21% of patients, respectively. On the first day of micafungin therapy, 2 patients presented with urticaria, which subsided after short-term steroid therapy without discontinuation of the study drug. A total of 4 patients died of septic shock during the study period, 1 additional patient died of septic shock and subsequent multiorgan failure including hyperbilirubinemia 54 days after discontinuation of the study drug.
Prophylaxis of Fungal Infections				
Cattaneo et al.[44] (2011) Caspofungin 50 to 70 mg/day vs standard prophylaxis regimens (SP) according to the physician's decision	RCT, MC Patients aged ≥18 years with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) who were at the start of induction chemotherapy	N=175 Variable duration	Primary: Incidence of probable/proven invasive fungal infections (IFIs) Secondary: Death rate related to IFIs and safety	Primary: The incidence of IFIs was 16.1% with caspofungin prophylaxis and 20.7% with SP (RR, 0.78; 95% CI, 0.42–1.46). Probable/proven and possible IFIs were diagnosed in 7.5% and 8.6% of patients with caspofungin versus 3.7% and 17.1% of patients with SP (RR, 2.06; 95% CI, 0.55–7.7 and RR, 0.5; 95% CI, 0.22–1.14, respectively). In the SP subgroup there were no differences in the incidence of IFIs according to the different type of prophylaxis received. Secondary: A total of 8.6% of patients died (caspofungin: 9.7%; SP prophylaxis: 7.3%; RR, 1.32; 95% CI, 0.49–3.56). In only one case, death attributable to probable/proven IFI. None of the patients receiving caspofungin died of toxicity, whereas one patient receiving itraconazole died of hepato-renal failure, possibly due to prophylaxis-related toxicity. Five patients experienced WHO grade >2 toxicity, with three receiving caspofungin and two itraconazole.
de Fabritiis et al.[36] (2007) Caspofungin 70 mg loading dose, then 50 mg IV daily from	OL, MC Patients ≥18 years of age who were undergoing allogeneic stem cell transplantation	N=18 Up to 31 months from stem cell reinfusion	Primary: Success of secondary prophylaxis (defined as the absence of documented	Primary: Of the 18 patients evaluable at day 30, 4 were considered stable, 12 improved and 2 progressed. Fifteen patients were evaluable at day 180 because three deaths occurred before day 30. Two patients were considered stable and 11 still improved at day 180, while 2 patients had their previous invasive fungal infection

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the start of the conditioning regimen until a stable engraftment of >1X10^9/l neutrophil cells Oral itraconazole 400 mg/day was given after caspofungin as maintenance therapy.	and had a previous probable or proven fungal infection		relapse of the fungal infection and the absence of new proven, probable or possible invasive fungal infection)	progress. Eleven patients were evaluable at 1 year of follow-up. No patient showed signs of previous invasive fungal infection progression. Two patients were stable and nine improved. At 31 months of follow-up, the probability of survival of the 18 patients submitted to allogeneic SCT with a previous invasive fungal infection was 45%. Three patients died due to leukemia relapse or progression; five patients died due to transplant-related complications with evidence of fungal infection in two patients. Transplant-related mortality of the 18 patients was 28.6%.
van Burik et al.[28] (2004) Micafungin 50 mg IV vs fluconazole 400 mg IV	RCT, DB, PRO Patients 6 months of age and older who were to undergo an allogeneic HSCT for any indication or an autologous HSCT for hematological malignancy and who were free from invasive fungal disease	N=882 4 week posttreatment follow-up	Primary: Treatment success (absence of proven, probable, or suspected fungal infection through the end of prophylaxis therapy and the absence of proven or probable fungal infection through the 4-week follow-up period)	Primary: The treatment success rate was significantly higher in the micafungin group compared to the fluconazole group (80% and 73.5%, respectively; P=0.03). There were 6 breakthrough infections due to *Candida* species; 4 in the micafungin group and 2 in the fluconazole group. There was 1 case of probable breakthrough aspergillosis in patients treated with micafungin and 7 cases in patients treated with fluconazole (P=0.071). There was 1 case of fusariosis in the micafungin group and 2 in the fluconazole group. There was 1 episode of zygomycosis in a micafungin-treated patient.
Hiramatsu et al.[39] (2008) Micafungin 150 mg IV daily vs fluconazole 400	RCT, OL Adult patients with a hematological malignancy who were undergoing high-dose combination chemotherapy with	N=104 4-week posttreatment follow-up	Primary: Treatment success (defined as the absence of proven, probable, or suspected systemic fungal infection through the end of	Primary: The overall treatment success rate for patients in the micafungin arm was comparable to that in the fluconazole arm (94.0% and 88.0%, respectively; 95% CI, -5.4 to 17.4; P=0.295). Suspected invasive fungal infections (IFIs) were reported to occur in 4% of patients in the micafungin arm and 12% of patients in the fluconazole arm (P=0.14). More fluconazole-treated patients received empirical antifungal therapy compared with micafungin-treated patients during the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg IV daily Patients received treatment within 48 hours of the transplant-related conditioning regimen.	autologous or allogeneic hematopoietic stem cell transplantation (HSCT)		prophylaxis therapy and as the absence of a proven or probable systemic fungal infection through the end of the 4-week posttreatment period)	post-treatment period only (12.0% vs 4.0%; P=0.14), although there was no significant difference. In total, 4.0% of micafungin-treated patients and 1.0% of fluconazole-treated patients died during course of the study. None of the deaths were related to the study drug.
Hashino et al.[42] (2008) Micafungin 100 mg IV daily beginning 14 days prior to allogenic STC vs fluconazole 400 mg IV/oral daily (historical control) Therapy was continued until hematological engraftment. Fluconazole 200 mg/day was given until the cessation of immuno-suppressants.	OL Adult patients with hematological and non-hematological malignancy undergoing allogeneic stem cell transplantation (STC)	N=44 11-80 days	Primary: Treatment success (defined as the absence of proven, probable, or possible invasive fungal infection [IFI] until day 21 after the SCT)	Primary: Treatment success was achieved in 87.8% of patients in the micafungin group and in 65.5% of the patients) in the fluconazole group (P=0.038). None of the patients in the micafungin group were diagnosed with proven or probable IFI. In the patients treated with fluconazole, there was one with disseminated candidiasis (caused by *Candida* krusei) and one with invasive pulmonary aspergillosis (IPA). Five patients were diagnosed as having possible IFI. Seven patients in the fluconazole group were diagnosed as having possible IFI.
Kusuki et al.[46] (2009) Micafungin 3	RETRO Children with neutropenia during	N=40 Variable duration	Primary: Treatment success (defined as absence of proven,	Primary: Successful prophylaxis was achieved in 123 of 131 patient-cycles (93.9%) for chemotherapy and 12 of 15 HSCTs (80.0%), and in 32 of 39 patients (82.1%) for chemotherapy and 11 of 14 HSCT patients (78.6%). A total of

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mg/kg once daily	chemotherapy or HSCT		probable, possible, or suspected IFI during prophylaxis therapy), duration of neutropenia, time to IFI, and adverse events	75.0% of patients had successful prevention of IFI. The median duration of neutropenia was 13 days for chemotherapy and 23 days for HSCT. The median duration of micafungin prophylaxis for these groups was 12 days and 21 days, respectively. Proven IFI was observed in one patient, who received micafungin prophylaxis for 62 days for prolonged neutropenia. No probable or possible IFI cases were observed. Suspected IFIs were observed in 10 cases: eight after chemotherapy and two after HSCT. No adverse events were association with micafungin.
Miscellaneous Infections				
Zaoutis et al.[31] (2009) Caspofungin 70 mg/m^2 on day 1, followed by 50 mg/m^2 daily thereafter as primary or salvage monotherapy	OL, MC Children 3 months to 17 years of age with proven or probable invasive aspergillosis, proven invasive candidiasis, or proven esophageal candidiasis	N=49 28-day posttreatment follow-up	Primary: Proportion of patients with a favorable response (complete or partial) at the end of caspofungin therapy	Primary: Five of 10 patients (50%) with invasive aspergillosis had a favorable clinical response at the end of caspofungin therapy. All 5 of the patients continued to have a favorable clinical response at both the 14- and 28-day posttreatment follow-up visits, 30 of 37 with invasive candidiasis, and 1 of 1 with esophageal candidiasis. Thirty of 37 patients (81.8%) with invasive candidiasis had a favorable response at the end of caspofungin therapy. One patient with invasive candidiasis relapsed during the 28-day follow-up period. One patient with esophageal candidiasis had complete resolution of esophageal and oropharyngeal lesions at the end of caspofungin therapy. All of the symptoms of infection had also resolved by day 32. This patient continued to have a favorable response at the 14- and 28-day posttreatment visits. Drug-related clinical or laboratory adverse events occurred in 27% and 35% of patients, respectively. There were no serious drug-related adverse events or discontinuations of caspofungin because of toxicity.
Tamura et al.[38] (2009) Micafungin 50-150	OL, MC Patients ≥16 years of age with	N=197 8 weeks	Primary: Overall response rate	Primary: The overall clinical response rate was 66.4% for patients with hematological diseases and 71.4% for those with HSCT, respectively.

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mg IV daily for ≥5 days up to 8 weeks	hematological diseases or hematopoietic stem cell transplantation (HSCT) and possible or proven fungal infections			The total response rate was 68.0%. The subset analysis showed no significant difference among various underlying diseases except for chronic leukemia, in which the response rate was very low, although the number of patients was only 8. All other patients experienced over 50% of response. There were eight patients with proven invasive fungal infections (IFIs) consisting of candidemia or esophageal candidiasis, seven of whom had favorable responses. Seventeen of 38 patients with probable IFIs responded to micafungin. Sixty-three patients with possible fungal infections defined by clinical symptoms and physical findings, and positive serological tests or imaging study received micafungin and 39 had favorable response. In patients with febrile neutropenia, 86.3% of patients had a favorable response. For patients with persistent neutropenia (neutrophils <500 cells/mL), the efficacy rate was 69.2%. The efficacy rate by the duration of neutropenia was as follows: 1/1 (100%) for less than 7 days, 4/7 (57.1%) for between 8 and 14 days, 1/2 (50.0%) for between 15 and 28 days and 3/3 (100%) for more than 29 days. The response rate in patients with or without antifungal pre-treatment was 70.1% and 63.5%, respectively. Thirty-two patients were treated with a combination of micafungin and other antifungal agents. The overall response rate was 78.1%. For patients with micafungin treatment alone, the response rate was 66.1%. The most frequent drug-related adverse event was the elevation of serum aminotransferase, renal dysfunction and electrolyte imbalance.
Mills et al.[48] (2009) Antifungal agents (azoles, amphotericin B,	MA Patients with invasive fungal infections	N=965 (11 trials) Variable duration	Primary: Global response rate Secondary: All-cause	Primary: For global response rate, the pooled estimate was 0.87 when azoles were compared to amphotericin B (95% CI, 0.78-0.96; P=0.007). When only fluconazole trials were compared to amphotericin B, there were similar effects (RR 0.82, 95% CI, 0.74–0.92; P=0.0009). The itraconazole versus amphotericin B trial (RR 0.90, 95% CI, 0.49–1.63; P=0.61) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
echinocandins)			mortality, fungal-attributable mortality, and adverse events	voriconazole versus amphotericin B trial (RR 0.99, 95% CI, 0.77–1.30; P=0.94) provided similar estimates. Two trials comparing echinocandins and amphotericin B demonstrated a pooled RR of 1.10 (95% CI, 0.99–1.23; P=0.08). The anidulafungin to fluconazole trial yielded a RR of 1.26 (95% CI, 1.06–1.51; P=0.001) in favor of anidulafungin; and micafungin to caspofungin (RR 1.00, 95% CI, 0.94– 1.08; P=0.21). Secondary: Seven trials comparing azoles and amphotericin B were pooled for all-cause mortality, which demonstrated a RR of 0.88 (95% CI, 0.74–1.05; P=0.17). Similar results were found when individual azoles were analyzed: fluconazole (5 trials) RR 0.92 (95% CI, 0.73–1.17; P=0.51; itraconazole (1 trials) RR 0.67, 95% CI, 0.74–1.05; P=0.20; voriconazole (1 trials) RR 0.85, 95% CI, 0.65–1.12; P=0.67). When echinocandins were compared to amphotericin B (2 trials), there was a pooled RR of 1.01 (95% CI, 0.84–1.20; P=0.93). Micafungin versus caspofungin resulted in a RR of 0.85 (95% CI, 0.96–1.11) in the direction of favor of caspofungin. Anidulafungin versus fluconazole resulted in a RR of 0.73 (95% CI, 0.48–1.10; P=0.34) in the direction of anidulafungin. When 5 trials comparing azoles to amphotericin B were pooled, a RR of 0.84 was found (95% CI, 0.49–1.42; P=0.51). When the 3 echinocandin trials versus amphotericin B were pooled, the RR was 1.16 (95% CI, 0.75–1.79; P=0.50). Anidulafungin versus fluconazole yielded a RR of 0.84 (95% CI, 0.48–1.47; P=0.88). To assess serious adverse events, 2 trials were pooled comparing azoles and amphotericin B, which showed a RR of 0.67 (95% CI, 0.55– 0.81; P≤0.0001) in favor of azoles. Two trials comparing echinocandins and amphotericin B were pooled, which showed a RR of 0.49 (95% CI, 0.37–0.66; P≤0.0001) in favor of the echinocandins. Micafungin and caspofungin had similar safety profiles (RR 0.94, 95% CI, 0.70–1.29). There was no significant difference between anidulafungin versus fluconazole (RR 0.90, 95% CI, 0.60–1.36; P=0.66).

Drug regimen abbreviations: IV=intravenously
Study abbreviations: CI=confidence interval, DB=double blind, DD=double dummy, DR=dose ranging, MC=multi-center, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk

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 Echinocandins

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Anidulafungin	injection	Eraxis®	$$$$$	N/A
Caspofungin	injection	Cancidas®	$$$$$	N/A
Micafungin	injection	Mycamine®	$$$$$	N/A

N/A=Not available

X. Conclusions

The echinocandins are approved for the treatment of *Candida* infections.[1-6] Caspofungin is also approved for the treatment of invasive aspergillosis, as well as empirical therapy for presumed fungal infections in febrile, neutropenic patients.[5] The echinocandins are only available in an injectable formulation and there are no generic products available.

The echinocandins are recommended as an alternative treatment option for patients with invasive aspergillosis and cutaneous aspergillosis.[7,51] However, empirical therapy with caspofungin is recommended for high-risk patients with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy.[7] For the treatment of candidiasis, guidelines recommend the use of an echinocandin as initial therapy in patients with moderate-to-severe candidemia and for patients who have had recent azole exposure.[8] They are also recommended for the empirical treatment of suspected invasive candidiasis, as well as for prophylaxis in patients with

chemotherapy-induced neutropenia and stem cell transplant patients with neutropenia.[8] They are considered an alternative treatment option for patients with chronic disseminated candidiasis, osteoarticular *Candida* infections, *Candida* endophthalmitis, cardiovascular *Candida* infections, oropharyngeal candidiasis and esophageal candidiasis.[8]

Several non-comparative trials have demonstrated that the echinocandins are effective for both the empirical and targeted treatment of systemic *Candida* infections and aspergillosis.[10-14,20,25,29-31,36-38,42] However, there are relatively few studies that directly compare the efficacy and safety of the echinocandins. Caspofungin and micafungin demonstrated similar clinical outcomes in patients with systemic candidiasis, as well as for the empirical treatment of febrile neutropenia.[35,45] Studies have also demonstrated comparable efficacy when the echinocandins were compared to antifungal agents in other classes.[19,21,23,26-27,32,34,39,41,43,47-48] Relatively few studies have demonstrated greater efficacy with the echinocandins compared to treatment with amphotericin B or fluconazole.[15-16,22,28,34,49]

There is insufficient evidence to support that one brand echinocandin is safer or more efficacious than another. 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 echinocandins 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 echinocandin 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Polyenes
AHFS Class 081428
May 9, 2012

I. Overview

The polyenes include oral nystatin and parenteral amphotericin B. These agents bind to the sterol component of the cell membrane, which leads to alterations in cell permeability and cell death.[1-5] While amphotericin B has a higher affinity for the fungal cell membrane, it can also bind to the cholesterol component of the mammalian cell leading to cytotoxicity.

Conventional amphotericin B (deoxycholate) is a broad spectrum antifungal agent that has been available for several decades. However, its use is associated with a high incidence of infusion-related adverse events and nephrotoxicity. There are three lipid formulations of amphotericin B that are currently available, which were developed to minimize toxicity associated with conventional amphotericin B. These include amphotericin B colloidal dispersion, amphotericin B lipid complex and amphotericin B liposome. Liposomal encapsulation, or incorporation in a lipid complex, can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug.[1-5] Different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect the functional properties of the various amphotericin B products.[1-5]

The polyenes that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The topical antifungals were previously reviewed with the skin and mucous membrane agents (AHFS 840408) and are not included in this review. Amphotericin B (conventional) and nystatin are available in a generic formulation. This class was last reviewed in November 2009.

Table 1. Polyenes Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amphotericin B	injection	N/A	amphotericin B
Amphotericin B cholesteryl sulfate complex	injection	Amphotec®	none
Amphotericin B lipid complex	injection	Abelcet®	none
Amphotericin B liposome	injection	AmBisome®	none
Nystatin	powder for suspension, suspension, tablet	N/A	nystatin

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

The polyenes 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 FDA-approved indications for the polyenes 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 anti-infective therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Organisms Susceptible to the Polyenes[1-5]

Organism	Amphotericin B	Amphotericin B Cholesteryl Sulfate Complex	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Aspergillus species	✔	✔	✔	✔	
Aspergillus fumigatus	✔	✔	✔	✔	
Blastomyces dermatitidis	✔			✔	
Blastomyces species			✔		
Candida albicans		✔	✔	✔	✔
Candida guillermondii			✔		
Candida krusei				✔	
Candida lusitaniae				✔	
Candida species	✔	✔	✔	✔	✔
Candida stellatoideae			✔		
Candida tropicalis			✔		
Coccidioides immitis	✔	✔		✔	
Coccidioides species			✔		
Cryptococcus neoformans	✔	✔		✔	
Cryptococcus species			✔		
Histoplasma capsulatum	✔			✔	
Histoplasma species			✔		
Leishmania donovani				✔	
Leishmania infantum				✔	
Leishmania species		✔			
Mucor mucedo	✔				
Paracoccidioides brasiliensis				✔	
Rhodotorula	✔				
Sporothrix schenckii	✔				

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Polyenes

Clinical Guideline	Recommendation(s)
American Thoracic Society (ATS): **Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients[7] (2011)**	Histoplasmosis (Immunocompetent Hosts with *Histoplasma*-related Pulmonary Nodules, Broncholithiasis, or Fibrosing Mediastinitis) • Among asymptomatic patients with pulmonary nodules in whom *Histoplasma* cannot be cultured, antifungal treatment is not recommended. • In most patients with broncholithiasis, antifungal treatment is not recommended. • In patients with fibrosing mediastinitis, some clinicians recommend itraconazole 200 mg twice daily for 12 weeks. In patients with radiographic or physiologic improvement after an initial 12 weeks of therapy, longer treatment, up to 12 months, is recommended. Histoplasmosis (Immunocompetent Hosts with Symptomatic, Progressive, or Severe Pulmonary Histoplasmosis) • In asymptomatic patients, no antifungal treatment is recommended. • In symptomatic patients with mild pulmonary histoplasmosis, who remain symptomatic after 3 weeks of observation, itraconazole 200 mg twice daily for up to 12 weeks is recommended. • In selected patients with mild to moderate pulmonary histoplasmosis, initiating treatment with itraconazole 200 mg twice daily rather than with amphotericin B is recommended. • In patients with severe pulmonary histoplasmosis, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed or until a cumulative dose of 2 g of amphotericin B is reached. In patients who improve clinically after initial treatment with amphotericin B, maintenance itraconazole 200 mg twice daily for at least 12 weeks is recommended. Histoplasmosis (Immunocompromised Hosts with Pulmonary Histoplasmosis or with Progressive or Disseminated Disease, or With Chronic Pulmonary Histoplasmosis) • In patients with mild to moderate histoplasmosis, itraconazole 200 mg three times daily for 3 days is recommended, followed by 200 mg twice daily for 12 months. • In patients with severe progressive disseminated histoplasmosis requiring hospitalization, amphotericin B 0.7–1.0 mg/kg/day (or a lipid formulation of amphotericin 3–5 mg/kg/d) is recommended until clinical improvement is observed or until a cumulative dose of 2 g of amphotericin B is reached. In patients who improve clinically after initial treatment with amphotericin B, itraconazole 200 mg twice daily for 12 months is recommended. • In patients with AIDS and progressive disseminated histoplasmosis who completed 12 months of initial itraconazole therapy, itraconazole 200 mg twice daily is recommended until effective immune reconstitution occurs. • In patients with chronic pulmonary histoplasmosis, itraconazole 200 mg twice daily for 12 to 24 months is recommended rather than no antifungal treatment. • In patients with severe chronic pulmonary histoplasmosis, initial treatment with amphotericin B is recommended over itraconazole. Sporotrichosis

Clinical Guideline	Recommendation(s)

	• In patients with mild to moderately severe pulmonary sporotrichosis, itraconazole 200 mg twice daily is recommended, with a total duration of therapy generally of 3 to 6 months based upon overall clinical response.
	• In patients with severe pulmonary sporotrichosis, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed or until a cumulative dose of 1 to 2 g of amphotericin B is reached, followed by itraconazole 200 mg twice daily, with total duration of therapy generally of 3 to 6 months based upon overall clinical response.
	<u>Blastomycosis (Immunocompetent Hosts)</u>
	• In patients with mild to moderate pulmonary blastomycosis, oral itraconazole 200 mg twice daily is recommended for 6 months.
	• In patients with severe pulmonary blastomycosis, amphotericin B 0.7–1.0 mg/kg/day daily is recommended until clinical improvement is observed, followed by continuation of amphotericin B 0.7–1.0 mg/kg three times weekly, until a cumulative dose of 1.5–2.5 g is reached. Once clinical improvement is observed, oral itraconazole 200 mg twice daily is recommended for 6 months.
	• In patients with pulmonary blastomycosis and bone involvement, it is recommended to prolong treatment with itraconazole to 12 months.
	• In patients with pulmonary blastomycosis and concomitant CNS involvement, the following are recommended:
	  o Liposomal amphotericin B 0.7 mg/kg/day until a cumulative dose of 2 g is reached
	  o Triazoles should not used as monotherapy for meningeal blastomycosis
	  o High dose intravenous or oral fluconazole 400–800 mg daily may be provided as an add-on therapy to intravenous amphotericin B in patients with severe or refractory disease, with the total duration of fluconazole therapy extended for at least 6 months.
	<u>Blastomycosis (Immunocompromised Hosts)</u>
	• In patients with severe pulmonary blastomycosis without CNS involvement, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed. Once clinical improvement is observed, oral itraconazole 200 mg twice daily is recommended for at least 12 months.
	• In patients with mild to moderate pulmonary blastomycosis without CNS involvement, oral itraconazole 200 mg twice daily is recommended for at least 12 months.
	• When AIDS is involved, oral itraconazole 200 mg/day is recommended indefinitely or until immunity is fully restored.
	• In patients with pulmonary blastomycosis and concomitant CNS involvement, the following are recommended:
	  o Combined therapy with amphotericin B 0.7 mg/kg/day together with intravenous or oral fluconazole 400–800 mg daily from the onset until clinical improvement is observed.
	  o Use of fluconazole for at least 12 months total after discontinuation of combined intravenous treatment with amphotericin B and high-dose fluconazole.
	  o Use of liposomal amphotericin B rather than amphotericin B deoxycholate should be considered due to theoretic better CNS penetration.
	  o Triazoles are not used as monotherapy.

Clinical Guideline	Recommendation(s)
	○ Patients with AIDS should continue to receive oral fluconazole 400 mg per day indefinitely or until immunity is restored. • In patients with pulmonary blastomycosis with new or progressing CNS involvement despite amphotericin B monotherapy, the following are recommended: ○ Combined therapy with liposomal amphotericin B 5 g/kg/day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day. ○ Fluconazole is used for at least 6 months in immunocompetent d fluconazole is used for at least 6 months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole. ○ Patients with AIDS receive oral fluconazole 400 mg daily indefinitely or until immunity is restored. • In critically ill patients with pulmonary blastomycosis, the following are recommended: ○ Combined therapy with amphotericin B (0.7–1.0 mg/kg amphotericin B deoxycholate or 5 mg/kg daily liposomal amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day. ○ Following the initial intravenous therapy, oral itraconazole is used for at least 6 months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and itraconazole. ○ After initial therapy is complete, patients with AIDS should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored. Voriconazole 200 mg twice daily may be used as an alternative to itraconazole. • In patients with pulmonary blastomycosis with new or progressing CNS involvement despite amphotericin B monotherapy, the following are recommended: ○ Combined therapy with liposomal amphotericin B 5 mg/kg/ day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day. ○ Fluconazole is used for at least 6 months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole. ○ Patients with AIDS receive oral fluconazole 400 mg daily indefinitely or until immunity is restored. ○ Voriconazole 200 mg twice daily may be considered as an alternative to fluconazole, though extensive disease-specific data are currently lacking. • In critically ill patients with pulmonary blastomycosis, the following are recommended: ○ Combined therapy with amphotericin B (0.7–1.0 mg/kg amphotericin B deoxycholate or 5 mg/kg daily liposomal amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day. ○ Following the initial intravenous therapy, oral itraconazole is used for at least 6 months in immunocompetent patients, and at least 12 months in immunocompromised patients, after

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	discontinuation of combined treatment with amphotericin B and itraconazole. o After initial therapy is complete, patients with AIDS should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored. o Voriconazole 200 mg twice daily may be considered as an alternative to itraconazole, though this is based largely on in vitro sensitivities and limited case based data. <u>Coccidioidomycosis (Immunocompetent Hosts)</u> • In most immunocompetent patients with primary pulmonary coccidioidomycosis and no additional risk factors for dissemination, we suggest no antifungal treatment. • In immunocompetent patients with primary pulmonary coccidioidomycosis and moderate to severe symptoms, or those in whom symptoms persist for more than 6 weeks, treatment with triazole antifungal drugs are recommended for at least 3 to 6 months or longer if symptoms and radiographic abnormalities persist. <u>Coccidioidomycosis (Immunocompromised Hosts and Others at Risk for Disseminated Disease)</u> • In many patients with pulmonary coccidioidomycosis and pulmonary nodules only, observation is recommended for at least 1 year without antifungal treatment. However, fluconazole (400 mg/d) or itraconazole (400 mg/d) may be considered during periods of significant immune suppression (i.e., chemotherapy, systemic corticosteroid therapy, or CD4 counts, 250/ml). • In patients with pulmonary coccidioidomycosis and pulmonary nodules who have additional risk factors for disseminated disease, patients with cavities, and those presenting with hemoptysis, treatment with triazole antifungal drugs are recommended, either fluconazole (400 mg/d) or itraconazole (400 mg/d). • For diffuse pulmonary coccidioidomycosis with significant impairment of gas exchange, initial liposomal amphotericin B (5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d) is recommended until clinical improvement, followed by fluconazole (400 mg/d) or itraconazole (400 mg/d) for at least another year. In patients with ongoing immune suppression, azole therapy may be continued indefinitely. • All patients, whether immunocompetent or immunocompromised, with any form of disseminated coccidioidomycosis require treatment. For non-meningeal disseminated disease, treatment with fluconazole (400 mg/d) or itraconazole (400 mg/d) is recommended for at least a year and until clinical improvement and stabilization. Itraconazole is preferred in bone disease. In severe or refractory cases, liposomal amphotericin B (5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d) may be initiated until clinical improvement, followed by fluconazole (400 mg/d) or itraconazole (400 mg/d) for at least another year. • In patients with meningitis, fluconazole (400–1,000 mg/d) or itraconazole (400–600 mg/d) for life. In patients with meningitis in whom treatment with triazole antifungal drugs failed, of intrathecal amphotericin B is recommended in select cases. <u>Paracoccidioidomycosis</u> • In critically ill patients with disseminated paracoccidioidomycosis, initial amphotericin B (0.7–1 mg/kg/d) therapy is recommended until clinical stabilization or until 2 g total dose administered. This may be followed by azole therapy as listed below. • In patients with disseminated paracoccidioidomycosis and mild to

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	moderate or slowly progressive symptoms, one of the following options is recommended until clinical stabilization and resolution of symptoms. The total duration of therapy must be individualized to clinical response, but generally therapy for 6 to 12 months or longer is employed. Potential regimens include: o Ketoconazole 200–400 mg daily o Itraconazole 100–400 mg daily o Sulfadiazine 4–6 g daily <u>Cryptococcosis (Immunocompetent Hosts)</u> • In asymptomatic immunocompetent patients with respiratory tract colonization by *C. neoformans*, no antifungal treatment is recommended. • In immunocompetent patients with pulmonary cryptococcosis and no evidence of other organ involvement, fluconazole 400 mg/day initially is recommended, tapering to 200 mg/day after clinical improvement is assured and with total treatment for 6 months. Alternatively, itraconazole 400 mg/day may be considered for 6 months. Fluconazole treatment is recommended for longer than 6 months in patients with documented *C. gattii* infection. <u>Cryptococcosis (Immunocompromised Hosts and Immunocompetent Hosts with Disseminated or CNS Involvement)</u> • In patients with disseminated cryptococcosis or CNS involvement, amphotericin B (0.7–1.0 mg/kg/d) plus flucytosine (100 mg/kg/d) is recommended for 2 weeks, then fluconazole or itraconazole (400 mg/d) for 8 to 10 weeks. Alternatively, amphotericin B (0.7–1.0 mg/kg/d) plus flucytosine (100 mg/kg/d) may be administered for 6 to 10 weeks in patients in whom azoles cannot be used. • In patients with disseminated cryptococcosis or CNS involvement, it is recommended that azoles not be used as monotherapy. • In patients with refractory disease not responding to fluconazole and itraconazole, voriconazole or posaconazole can be considered as salvage therapy on a case by case basis. • In patients with AIDS and CD4+ T cell count less than 200/ml who have disseminated cryptococcosis or CNS involvement, fluconazole 200 mg/day is recommended to be used indefinitely, after successful primary therapy as outlined above, or until CD4+ T cell count is greater than 200/ml, HIV RNA is undetectable and sustained for 3 months, and the patient is stable for 1 to 2 years. <u>Invasive Aspergillosis</u> • When invasive disease is suspected or confirmed, prompt, aggressive antifungal treatment is essential. • Although amphotericin B deoxycholate had historically been the ‘‘gold standard’’ for the treatment of invasive aspergillosis, most clinicians and the most recent IDSA guidelines recommend voriconazole as the primary treatment option. • There are no definitive data or consensus opinions indicating improved efficacy of any of the lipid amphotericin formulations over amphotericin B deoxycholate in the treatment of invasive aspergillosis. Thus, the best indication for using a lipid formulation appears to be for reducing renal toxicity to allow the administration of high doses of amphotericin for a prolonged time. • Voriconazole has recently emerged as a standard therapy for the treatment of invasive aspergillosis, based on the results of a randomized trial comparing the outcomes to amphotericin B deoxycholate; however, whether outcomes are superior to lipid

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	formulations of amphotericin B has not been determined. In many instances voriconazole may be considered the treatment of choice the patient can be transitioned to oral formulations of this drug.
	• Oral itraconazole is not recommended for initial therapy for invasive aspergillosis. However, after disease progression is arrested with either voriconazole or amphotericin, the patient can be transitioned to oral itraconazole.
	• Caspofungin use in invasive aspergillosis is largely limited to salvage therapy, often in combination with other antifungal agents, after primary therapy with amphotericin-based regimens have failed.
	• There is currently insufficient clinical support to recommend combination therapy, although many clinicians are employing this approach as a ‘‘last option,’’ or in settings of particularly advanced disease.
	<u>Aspergillomas</u>
	• In patients with aspergillomas, it is recommended that antifungal agents not be used.
	• Antifungals should only be used only in patients suspected of having a component of semi-invasive disease.
	<u>Hypersensitivity Pneumonitis Related to *Aspergillus*</u>
	• In patients with hypersensitivity pneumonitis, it is recommended that antifungal therapy not be used.
	<u>Invasive Pulmonary Aspergillosis</u>
	• In patients with invasive pulmonary aspergillosis, the following are recommended:
	  o Intravenous voriconazole 6 mg/kg every 12 hours for 1 day, followed by 4 mg/kg every 12 hours until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400–600 mg/day until resolution or stabilization of all clinical and radiographic manifestations OR
	  o Intravenous liposomal amphotericin B 3–5 mg/kg/day until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400–600 mg/day until resolution or stabilization of all clinical and radiographic manifestation
	• In patients with invasive pulmonary aspergillosis who have failed front line therapy and are requiring salvage therapy, the following are recommended:
	  o Intravenous caspofungin 70 mg on Day 1 and 50 mg/day intravenously thereafter, or intravenous micafungin 100– 150 mg/day until improvement, followed by oral voriconazole 200 mg every 12 hours or oral itraconazole 400–600 mg/day until resolution of disease OR
	  o Posaconazole 200 mg four times per day initially, then 400 mg twice daily orally after stabilization of disease
	<u>Chronic Necrotizing Aspergillosis</u>
	• In patients with chronic necrotizing aspergillosis, with mild to moderate disease, voriconazole (200 mg every 12 h) or itraconazole (400–600 mg/d) is recommended until resolution or stabilization of all clinical and radiographic manifestations.
	• If clinically severe, consider beginning therapy of chronic necrotizing aspergillosis with either liposomal amphotericin B or IV voriconazole as described above for invasive disease.
	• In select patients at high risk of invasive fungal infection, some anti-

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	Aspergillus prophylaxis is warranted. Data support the use of posaconazole 200 mg orally three times daily until recovery from neutropenia and clinical remission is established. Other prophylaxis approaches have utilized itraconazole, micafungin, and inhaled liposomal amphotericin B.
	Candidemia
	• Candidemia should be treated with antifungal agents, selecting one of the following agents: fluconazole, an amphotericin B formulation, an echinocandin, voriconazole, or the combination regimen of fluconazole and amphotericin B.
	• For patients who are clinically stable and have not recently received azole therapy, the following are recommended:
	  o Fluconazole (400 mg/d or ~6 mg/kg/d) OR
	  o Caspofungin (70 mg loading dose day 1, then 50 mg/d) OR
	  o Micafungin (100 mg/d) OR
	  o Anidulafungin (200 mg on day 1, then 100 mg/d).
	• For patients who are clinically unstable and for whom identification of the *Candida* species in the blood is unknown, there is no definitive recommendation. Several options are available and include:
	  o Amphotericin B deoxycholate (0.6–1.0 mg/kg/d) or a lipid formulation of amphotericin B (3–5 mg/kg/d) OR
	  o High-dose fluconazole (800 mg/kg/d or z 12 mg/kg/d) OR
	  o Caspofungin (70 mg loading dose day 1, then 50 mg/d) OR
	  o Micafungin (100 mg/d) OR
	  o Anidulafungin (200 mg on day 1, then 100 mg/d) OR
	  o Voriconazole (6 mg/kg/12 h X 2, then 3 mg/kg/12 h) OR
	  o A combination regimen with fluconazole (800 mg/d) and amphotericin B (0.6– 1.0 mg/kg/d, for the first 5–6 d)
	• For *C. albicans* and also possibly *C. tropicalis*, the drugs of choice are fluconazole (400 mg/d), amphotericin B (0.6–1.0 mg/kg/d), and an echinocandin.
	• For *C. parapsilosis*, the drugs of choice are fluconazole (400 mg/d) or amphotericin B (0.6–1.0 mg/kg/d).
	• For *C. glabrata*, the drugs of choice are an echinocandin or amphotericin B. High-dose fluconazole (800 mg/d) may be a suitable alternative.
	• For *C. krusei*, the drugs of choice are an echinocandin or amphotericin B.
	• For *C. lusitaniae*, fluconazole is the preferred therapy.
	• Lipid formulations of amphotericin B are usually indicated for patients intolerant of, or refractory to, conventional antifungal therapy
	Other Fungi
	• In patients with zygomycosis, lipid formulations of amphotericin B are recommended at 5 mg/kg/day or amphotericin B deoxycholate at 0.7–1.0 mg/kg/day.
	• In patients who are intolerant of, or refractory to, amphotericin B, posaconazole 200 mg orally four times per day is recommended.

Infectious Diseases Society of America (IDSA): **Treatment of Aspergillosis[9] (2008)**	Invasive Pulmonary Aspergillosis • For primary treatment of invasive pulmonary aspergillosis, IV or oral voriconazole is recommended for most patients. For seriously ill patients, the parenteral formulation is recommended. • Liposomal amphotericin B (L-AMB) may be considered as alternative primary therapy in some patients. For salvage therapy, agents include lipid formulations of amphotericin (LFABs), posaconazole, itraconazole, caspofungin, or micafungin.

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	• In the absence of a well-controlled, prospective clinical trial, routine administration of combination therapy for primary therapy is not routinely recommended. For salvage therapy, an additional antifungal agent might be added to current therapy, or combination antifungal drugs from different classes other than those in the initial regimen may be used. • For patients with successfully treated invasive aspergillosis who will require subsequent immunosuppression, resumption of antifungal therapy can prevent recurrent infection. <u>Tracheobronchial Aspergillosis</u> • Voriconazole is recommended as initial therapy in the treatment of tracheobronchial aspergillosis. • Because the use of deoxycholate amphotericin B (D-AMB) may result in increased nephrotoxicity in association with calcineurin inhibitors, an LFAB is recommended if a polyene is considered in the patient (e.g., lung transplant recipient). <u>Aspergillosis of the CNS</u> • The weight of evidence supports voriconazole as the primary recommendation for systemic antifungal therapy of CNS aspergillosis. • Itraconazole, posaconazole, or LFAB are recommended for patients who are intolerant or refractory to voriconazole. <u>Invasive Sinonasal Aspergillosis</u> • If the infection is known to be due to *Aspergillus* species, voriconazole should be initiated. • If the etiological organism is not known or histopathologic examination is still pending, an amphotericin B (AMB) formulation should be initiated in anticipation of possible sinus zygomycosis. <u>*Aspergillus* Osteomyelitis and Septic Arthritis</u> • Combined medical and surgical intervention is recommended for management of *Aspergillus* osteomyelitis and arthritis. • Although there is currently limited experience with voriconazole for treatment of *Aspergillus* osteomyelitis, voriconazole appears to be effective for this indication. • Historically, AMB has been used and would be appropriate therapy. <u>*Aspergillus* Endophthalmitis and *Aspergillus* Keratitis</u> • Following a diagnostic vitreal tap, IV AMB and, where appropriate, intravitreal AMB plus pars plana vitrectomy may be sight saving in *Aspergillus* endophthalmitis. • Voriconazole administered intravitreally or systemically is an alterative regimen. Management of *Aspergillus* keratitis requires emergency ophthalmologic intervention with ophthalmologic examination, topical antifungal therapy, and systemic antifungal therapy with AMB, voriconazole, or itraconazole. <u>Cutaneous Aspergillosis</u> • Therapy for secondary cutaneous lesions reflects that of disseminated infection, with systemic voriconazole recommended as primary therapy. • Alternative agents include L-AMB, posaconazole, itraconazole, or an echinocandin. <u>*Aspergillus* Peritonitis</u> • Removal of peritoneal dialysis catheter and intraperitoneal dialysis with AMB, in addition to IV administration of AMB, are recommended. • Itraconazole or an extended-spectrum azole (voriconazole or

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	posaconazole) may be used as a salvage therapy. Esophageal and Gastrointestinal Aspergillosis • Once a diagnosis is established, medical and surgical therapy is needed to prevent the complications of potentially fatal hemorrhage, perforation, obstruction, and infarction. • Systemic antifungal therapy, as used for disseminated invasive aspergillosis, is appropriate. Hepatic Aspergillosis • Medical therapy of hepatic aspergillosis should be considered as initial therapy. • For extrahepatic or perihepatic biliary obstruction, surgical intervention is warranted. Renal Aspergillosis • Because none of these agents is excreted primarily into the pelvis of the kidney or urine, the management of pelvicalyceal and ureteral infection may require nephrostomy with instillation of AMB. Empirical Antifungal Therapy of Neutropenic Patients • Empirical antifungal therapy with AMB, an LFAB, itraconazole, voriconazole, or caspofungin is recommended for high-risk patients with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for the Management of Blastomycosis[10] (2008)**	Pulmonary Blastomycosis • For moderately severe to severe disease, initial treatment with a lipid formulation of amphotericin B (AmB) or AmB deoxycholate for 1–2 weeks, followed by oral itraconazole for a total of 6–12 months is recommended. Disseminated Extrapulmonary Blastomycosis • For moderately severe to severe disease, lipid formulation AmB or AmB deoxycholate for 1–2 weeks, followed by oral itraconazole for a total of at least 12 months is recommended. CNS Blastomycosis • AmB, given as a lipid formulation over 4–6 weeks, followed by an oral azole is recommended. Treatment for Immunosuppressed Patients with Blastomycosis • AmB, given as a lipid formulation or AmB deoxycholate for 1–2 weeks is recommended as initial therapy for patients who are immunosuppressed, including those with AIDS. Treatment for Blastomycosis in Pregnant Women and in Children • During pregnancy, lipid formulation AmB is recommended. Azoles should be avoided because of possible teratogenicity. • If the newborn shows evidence of infection, treatment is recommended with AmB deoxycholate. • For children with severe blastomycosis, AmB deoxycholate or lipid formulation AmB is recommended for initial therapy, followed by oral itraconazole for a total of 12 months.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for the Management of Candidiasis[11] (2009)**	Candidemia in Non-neutropenic Patients • Fluconazole or an echinocandin (caspofungin, micafungin or anidulafungin) is recommended as initial therapy for most adult patients. • Amphotericin B deoxycholate (AmB-d) or a lipid formulation of AmB (LFAmB) are alternatives if there is intolerance to or limited availability of other antifungals. Transition from AmB-d or LFAmB to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *C. albicans*) and who are

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	clinically stable. Empirical Treatment for Suspected Invasive Candidiasis in Non-neutropenic Patients • Empirical therapy for suspected candidiasis in non-neutropenic patients is similar to that for proven candidiasis. Fluconazole, caspofungin, anidulafungin, or micafungin is recommended as initial therapy. • AmB-d or LFAmB are alternatives if there is intolerance to other antifungals or limited availability of other antifungals. Candidemia in Neutropenic Patients • An echinocandin or LFAmB is recommended for most patients. • For infections due to *C. glabrata*, an echinocandin is preferred. LFAmB is an alternative treatment option. • For infections due to *C. parapsilosis*, fluconazole or LFAmB is preferred as initial therapy. Empirical Treatment for Suspected Invasive Candidiasis in Neutropenic Patients • LFAmB, caspofungin, or voriconazole are recommended. • AmB-d is an effective alternative, but there is a higher risk of toxicity with this formulation than with LFAmB. Treatment for Neonatal Candidiasis • AmB-d is recommended for neonates with disseminated candidiasis. If urinary tract involvement is excluded, LFAmB can be used. Fluconazole is a reasonable alternative. Urinary Tract Infections – Asymptomatic Candiduria • Treatment is not recommended unless the patient belongs to a group at high risk of dissemination. Elimination of predisposing factors often results in resolution of candiduria. • High-risk patients include neutropenic patients, infants with low birth weight, and patients who will undergo urologic manipulations. Neutropenic patients and neonates should be managed as described for invasive candidiasis. For those patients undergoing urologic procedures, fluconazole or AmB-d for several days before and after the procedure is recommended. Urinary Tract Infections – Symptomatic Candiduria • For candiduria with suspected disseminated candidiasis, treatment as described for candidemia is recommended. • For cystitis due to a fluconazole-susceptible *Candida* species, oral fluconazole for 2 weeks is recommended. For fluconazole-resistant organisms, AmB-d for 1–7 days or oral flucytosine for 7–10 days are alternatives. AmB-d bladder irrigation is generally not recommended but may be useful for treatment of patients with fluconazole-resistant *Candida* species, especially *C. glabrata*. • For pyelonephritis due to fluconazole-susceptible organisms, oral fluconazole daily for 2 weeks is recommended. For patients with fluconazole-resistant *Candida* strains, especially *C. glabrata*, alternatives include AmB-d with or without flucytosine or flucytosine alone for 2 weeks. • For fungus balls, surgical intervention is strongly recommended in non-neonates. Fluconazole is recommended. AmB-d with or without flucytosine is an alternative. If access to the renal collecting system is available, an adjunct to systemic therapy is irrigation with AmB-d. Treatment duration should be until symptoms have resolved and urine cultures no longer yield *Candida* species. Chronic Disseminated Candidiasis

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	• Fluconazole is recommended for clinically stable patients. LFAmB or AmB-d can be used to treat acutely ill patients or patients with refractory disease. Induction therapy with AmB for 1–2 weeks, followed by oral fluconazole is also recommended. Osteoarticular Candida Infections • For osteomyelitis, fluconazole for 6–12 months or LFAmB for at least 2 weeks is recommended, followed by fluconazole daily for 6–12 months. Alternatives include an echinocandin or AmB-d for at least 2 weeks, followed by fluconazole for 6–12 months. • For septic arthritis, fluconazole for at least 6 weeks or LFAmB for at least 2 weeks is recommended, followed by fluconazole. Alternatives include an echinocandin or AmB-d for at least 2 weeks, followed by fluconazole for the remainder of therapy. • For infection involving a prosthetic device, device removal is recommended for most cases. Therapy for at least 6 weeks with fluconazole, LFAmB, an echinocandin, or AmB-d is recommended. If the device cannot be removed, chronic suppression with fluconazole is recommended. Central Nervous System Candidiasis • LFAmB with or without flucytosine is recommended for the initial several weeks of treatment. • Fluconazole is recommended as step-down therapy after the patient responds to initial treatment with LFAmB and flucytosine. Therapy should continue until all signs and symptoms, CSF abnormalities, and radiologic abnormalities have resolved. Candida Endophthalmitis • AmB-d combined with flucytosine is recommended for advancing lesions or lesions threatening the macula. Fluconazole is an acceptable alternative for less severe endophthalmitis. LFAmB, voriconazole, or an echinocandin can be used to treat patients who are intolerant of or experiencing treatment failure with AmB-d in combination with flucytosine or fluconazole. Cardiovascular Candida Infections • For native valve endocarditis, LFAmB with or without flucytosine is recommended. Alternatives include AmB-d with or without flucytosine or an echinocandin (caspofungin or anidulafungin). Step-down therapy to fluconazole should be considered among patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. Valve replacement is recommended, and treatment should continue for at least 6 weeks after valve replacement and should continue for a longer duration in patients with perivalvular abscesses and other complications. • For patients who cannot undergo valve replacement, long-term suppression with fluconazole is recommended. • For prosthetic valve endocarditis (PVE), the recommendations above apply, and suppressive therapy should be lifelong if valve replacement is not possible. • For pericarditis, LFAmB, AmB-d, an echinocandin, or fluconazole for as long as several months, in combination with either a pericardial window or pericardiectomy, is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to AmB or an echinocandin and who are clinically stable. • For myocarditis, treatment as for endocarditis (as stated above) is recommended. • For suppurative thrombophlebitis, catheter removal and incision and

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	drainage or resection of the vein, if feasible, is recommended. LFAmB, AmB-d, fluconazole, or an echinocandin for at least 2 weeks after candidemia has cleared is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to AmB or an echinocandin and who are clinically stable. Resolution of the thrombus can be used as evidence to discontinue antifungal therapy if clinical and culture data are supportive. • For pacemaker and implantable cardiac defibrillator wire infections, removal of the entire device and systemic antifungal therapy with LFAmB with or without flucytosine, AmB-d with or without flucytosine, or an echinocandin is recommended. Step-down therapy to fluconazole should be considered for patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. For infections limited to generators and/or pockets, 4 weeks of antifungal therapy after removal of the device is recommended. For pacemaker and implantable cardiac defibrillator wire infections, at least 6 weeks of antifungal therapy after wire removal is recommended. • For ventricular assist devices that cannot be removed, treatment with LFAmB, AmB-d, or an echinocandin is recommended. After candidemia has cleared and the patient has responded clinically, fluconazole is recommended as step-down therapy. Chronic suppressive therapy with fluconazole is warranted until the device is removed. <u>Oropharyngeal Candidiasis</u> • For mild disease, clotrimazole troches, nystatin suspension, or nystatin pastilles for 7–14 days is recommended. • For moderate to severe disease, oral fluconazole for 7–14 days is recommended. • For fluconazole-refractory disease, either itraconazole solution or posaconazole suspension for up to 28 days are recommended. Voriconazole or AmB-d are recommended when treatment with other agents has failed. Intravenous echinocandin or AmB-d can be used in treating patients with refractory disease. • Chronic suppressive therapy is usually unnecessary for patients with HIV infection. If suppressive therapy is required, fluconazole 3 times weekly is recommended. Treatment with HAART is recommended to reduce recurrent infections. • For denture-related candidiasis, disinfection of the denture, in addition to antifungal therapy, is recommended. <u>Esophageal Candidiasis</u> • Systemic antifungal therapy is always required. Oral fluconazole for 14–21 days is recommended. Intravenous fluconazole, AmB-d, or an echinocandin should be used for patients who cannot tolerate oral therapy. A diagnostic trial of antifungal therapy is appropriate before performing an endoscopic examination. • For fluconazole-refractory disease, itraconazole solution, posaconazole suspension, or voriconazole (administered intravenously or orally) for 14– 21 days is recommended. Micafungin, anidulafungin, or AmB-d are acceptable alternatives. • Suppressive therapy with fluconazole is recommended for recurrent infections. • In patients with AIDS, treatment with HAART is recommended to reduce recurrent infections. <u>Antifungal Prophylaxis for Solid-Organ Transplant Recipients</u>

Clinical Guideline	Recommendation(s)
	• For solid-organ transplant recipients, fluconazole or liposomal AmB (L-AmB) is recommended as postoperative antifungal prophylaxis for liver, pancreas, and small bowel transplant recipients at high risk of candidiasis.
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Treatment of Coccidioidomycosis[12] (2005)**	<u>Uncomplicated Acute Coccidioidal Pneumonia</u> • Commonly prescribed therapies include oral azole antifungal agents. Courses of therapy are typically administered for 3 to 6 months. • During pregnancy, amphotericin B is the treatment of choice because fluconazole (and likely other azole antifungals) are teratogenic. <u>Diffuse Pneumonia</u> • Therapy is usually begun either with amphotericin B or high-dose fluconazole. • Amphotericin B is more frequently used as initial therapy if significant hypoxia is present or if deterioration is rapid. • Several weeks of therapy are often required to produce clear evidence of improvement. After this time, amphotericin B therapy may be discontinued and replaced with treatment with an oral azole antifungal. • In combination, the total length of therapy should be at least 1 year, and for patients with severe immunodeficiency, oral azole therapy should be continued as secondary prophylaxis. <u>Symptomatic Pulmonary Cavity Infections</u> • Complications of coccidioidal cavities include local discomfort, superinfection with other fungi or possibly bacteria, or hemoptysis. Should these complications occur, oral therapy with azole antifungals may result in improvement, although recurrence of symptoms may occur on cessation of therapy. • Rupture of a coccidioidal cavity into the pleural space, resulting in a pyopneumothorax, is an infrequent but serious complication of coccidioidal pneumonia. In young, otherwise-healthy patients, surgical closure by lobectomy with decortication is the preferred management. • Antifungal therapy is recommended for treatment, particularly in cases with delay of diagnosis and coexistent diseases. • For patients in whom the diagnosis was delayed a week or more, or for patients in whom there are coexistent diseases, management approaches are less uniform and may include courses of therapy with amphotericin B or oral azole antifungal drugs prior to surgery or chest tube drainage without surgery. <u>Chronic Progressive Fibrocavitary Pneumonia</u> • Initial treatment with oral azole antifungal agents is recommended. • If the patient improves sufficiently, therapy should be continued for at least 1 year. If therapy is not satisfactory, switching to an alternative azole antifungal, raising the dosage of the azole, or therapy with amphotericin B are alternative strategies. • Surgical resection may be a useful option for refractory lesions that are well localized or in cases in which significant hemoptysis has occurred. <u>Non-meningeal Disseminated Infection (Extrapulmonary)</u> • Initial therapy is usually initiated with oral azole antifungal agents. • Amphotericin B is recommended for alternative therapy, especially if lesions are appearing to worsen rapidly and are in particularly critical locations, such as the vertebral column. • In patients experiencing failure of conventional deoxycholate amphotericin B therapy, or experiencing intolerable drug-related toxicities, lipid amphotericin B formulations have been demonstrated

Clinical Guideline	Recommendation(s)
	to be safe and to cause less nephrotoxicity and may be considered. • Combination therapy with amphotericin B and an azole has been administered to some patients, especially when infection is widespread or in cases in which there has been disease progression during treatment with a single agent. Although combination therapy may improve responses, there is no evidence that such an approach is more effective than treatment with a single agent. <u>Meningeal Disseminated Infection (Extrapulmonary)</u> • Therapy with oral fluconazole is preferred by most clinicians. Itraconazole, administered in dosages of 400–600 mg per day, has also been reported to be comparably effective. • Some physicians also initiate therapy with intrathecal amphotericin B in addition to an azole on the basis that responses are more prompt with this approach. Patients who respond to azole therapy should continue this treatment indefinitely. Patients who don't respond to fluconazole or itraconazole are candidates for intrathecal amphotericin B therapy with or without continuation of azole treatment.

Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for the Management of Cryptococcal Disease[13] (2010)**	<u>Cryptococcal Meningoencephalitis (HIV-Infected Individuals)</u>
	• Primary therapy: induction and consolidation:
	  ○ Amphotericin B (AmB) deoxycholate (AmBd) (0.7–1.0 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses; IV formulations may be used in severe cases and in those without oral intake where the preparation is available) for at least 2 weeks, followed by fluconazole (400 mg [6 mg/kg] per day orally) for a minimum of 8 weeks.
	  ○ Lipid formulations of AmB (LFAmB), including liposomal AmB (3–4 mg/kg per day IV) and AmB lipid complex (ABLC) (5 mg/kg per day IV) for at least 2 weeks, could be substituted for AmBd among patients with or predisposed to renal dysfunction.
	• Alternative regimens for induction and consolidation (listed in order of highest recommendation top to bottom):
	  ○ AmBd (0.7–1.0 mg/kg per day IV), liposomal AmB (3–4 mg/kg per day IV), or ABLC (5 mg/kg per day IV) for 4–6 weeks. Liposomal AmB has been given safely at 6 mg/kg per day IV in cryptococcal meningoencephalitis and could be considered in the event of treatment failure or high–fungal burden disease.
	  ○ AmBd (0.7 mg/kg per day IV) plus fluconazole (800 mg per day orally) for 2 weeks, followed by fluconazole (800 mg per day orally) for a minimum of 8 weeks.
	  ○ Fluconazole (≥800 mg per day orally; 1200 mg per day is favored) plus flucytosine (100 mg/kg per day orally) for 6 weeks.
	  ○ Fluconazole (800–2000 mg per day orally) for 10–12 weeks; a dosage of ≥1200 mg per day is encouraged if fluconazole alone is used.
	  ○ Itraconazole (200 mg twice per day orally) for 10–12 weeks, although use of this agent is discouraged.
	<u>Non-Meningeal, Pulmonary Cryptococcosis (Immunosuppressed):</u>
	• For mild-to-moderate symptoms, absence of diffuse pulmonary infiltrates, absence of severe immunosuppression, and negative results of a diagnostic evaluation for dissemination, use fluconazole (400 mg [6 mg/kg] per day orally) for 6–12 months.
	• In HIV-infected patients who are receiving HAART with a CD4 cell

Clinical Guideline	Recommendation(s)
	count >100 cells/µL and a cryptococcal antigen titer that is ≤1:512 and/or not increasing, consider stopping maintenance fluconazole after 1 year of treatment. Cryptococcal Meningoencephalitis (Non–HIV-Infected, Non-transplant Hosts) • AmBd (0.7–1.0 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for at least 4 weeks for induction therapy. The 4-week induction therapy is reserved for persons with meningoencephalitis without neurological complications and cerebrospinal fluid (CSF) yeast culture results that are negative after 2 weeks of treatment. For AmBd toxicity issues, LFAmB may be substituted in the second 2 weeks. In patients with neurological complications, consider extending induction therapy for a total of 6 weeks, and LFAmB may be given for the last 4 weeks of the prolonged induction period. Then, start consolidation with fluconazole (400 mg per day) for 8 weeks. • If patient is AmBd intolerant, substitute liposomal AmB (3–4 mg/kg per day IV) or ABLC (5 mg/kg per day IV). • If flucytosine is not given or treatment is interrupted, consider lengthening AmBd or LFAmB induction therapy for at least 2 weeks. • In patients at low risk for therapeutic failure, consider induction therapy with combination of AmBd plus flucytosine for only 2 weeks, followed by consolidation with fluconazole (800 mg [12 mg/kg] per day orally) for 8 weeks. • After induction and consolidation therapy, use maintenance therapy with fluconazole (200 mg [3 mg/kg] per day orally) for 6–12 months. Non-Meningeal, Pulmonary Cryptococcosis (Non-Immunosuppressed): • For mild-to-moderate symptoms, administer fluconazole (400 mg per day orally) for 6–12 months; persistently positive serum cryptococcal antigen titers are not criteria for continuance of therapy. • For severe disease, treat similarly to CNS disease. • Itraconazole (200 mg twice per day orally), voriconazole (200 mg twice per day orally), and posaconazole (400 mg twice per day orally) are acceptable alternatives if fluconazole is unavailable or contraindicated. Organ Transplant Recipients • For central nervous system (CNS) disease, liposomal AmB (3–4 mg/kg per day IV) or ABLC (5 mg/kg per day IV) plus flucytosine (100 mg/kg per day in 4 divided doses) for at least 2 weeks for the induction regimen, followed by fluconazole (400–800 mg [6–12 mg/kg] per day orally) for 8 weeks and by fluconazole (200–400 mg per day orally) for 6–12 months. If induction therapy does not include flucytosine, consider LFAmB for at least 4–6 weeks of induction therapy, and liposomal AmB (6 mg/kg per day) might be considered in high–fungal burden disease or relapse. • For mild-to-moderate non-CNS disease, fluconazole (400 mg [6 mg/kg] per day) for 6–12 months. • For moderately severe–to-severe non-CNS or disseminated disease without CNS involvement, treat the same as CNS disease. • In the absence of any clinical evidence of extrapulmonary or disseminated cryptococcosis, severe pulmonary disease is treated the same as CNS disease. For mild-to-moderate symptoms without diffuse pulmonary infiltrates, use fluconazole (400 mg [6 mg/kg] per day) for 6–12 months. • Fluconazole maintenance therapy should be continued for at least 6–12

Clinical Guideline	Recommendation(s)
	months. Cryptococcal Meningoencephalitis (Management of Complications - Persistence) • Reinstitute induction phase of primary therapy for longer course (4–10 weeks). • Consider increasing the dose if the initial dosage of induction therapy was ≤0.7 mg/kg IV of AmBd per day or ≤3 mg/kg of LFAmB per day, up to 1 mg/kg IV of AmBd per day or 6 mg/kg of liposomal AmB per day; in general, combination therapy is recommended. • If the patient is polyene intolerant, consider fluconazole (≥800 mg per day orally) plus flucytosine (100 mg/kg per day orally in 4 divided doses). • If patient is flucytosine intolerant, consider AmBd (0.7 mg/kg per day IV) plus fluconazole (800 mg [12 mg/kg] per day orally). • Use of intrathecal or intraventricular AmBd is generally discouraged and is rarely necessary. Cerebral Cryptococcomas • Induction therapy with AmBd (0.7–1 mg/kg per day IV), liposomal AmB (3–4 mg/kg per day IV), or ABLC (5 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for at least 6 weeks. • Consolidation and maintenance therapy with fluconazole (400–800 mg per day orally) for 6–18 months. Non-Meningeal, Non-Pulmonary Cryptococcosis • If CNS disease is ruled out, fungemia is not present, infection occurs at single site, and there are no immunosuppressive risk factors, consider fluconazole (400 mg [6 mg/kg] per day orally) for 6–12 months.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for the Management of Patients with Histoplasmosis[14] (2007)**	Moderately Severe to Severe Acute Pulmonary Histoplasmosis (Adults) • Lipid formulation of amphotericin B for 1–2 weeks followed by itraconazole for 12 weeks is recommended. • The deoxycholate formulation of amphotericin B is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity. Acute Pulmonary Histoplasmosis (Children) • Treatment indications and regimens are similar to those for adults, except that amphotericin B deoxycholate is usually well tolerated, and the lipid preparations are not preferred. Progressive Disseminated Histoplasmosis (Adults) • For moderately severe to severe disease, liposomal amphotericin B is recommended for 1–2 weeks, followed by oral itraconazole for at least 12 months. • Substitution of another lipid formulation may be preferred in some patients because of tolerability. • The deoxycholate formulation of amphotericin B is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity. Progressive Disseminated Histoplasmosis (Children) • Amphotericin B deoxycholate (1.0 mg/kg daily for 4– 6 weeks) is recommended. • Amphotericin B deoxycholate (1.0 mg/kg daily for 2– 4 weeks) followed by itraconazole (5.0–10.0 mg/kg daily in 2 divided doses) to complete 3 months of therapy is an alternative. CNS Histoplasmosis • Liposomal amphotericin B for 4–6 weeks followed by itraconazole for at least 1 year and until resolution of CSF abnormalities, including *Histoplasma* antigen levels, is recommended.

Clinical Guideline	Recommendation(s)
	Histoplasmosis in Pregnancy • Lipid formulation amphotericin B is recommended. The deoxycholate formulation of amphotericin B is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity. • If the newborn shows evidence for infection, treatment is recommended with amphotericin B deoxycholate.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for the Management of Sporotrichosis[15] (2007)**	Osteoarticular Sporotrichosis • Itraconazole is recommended for at least 12 months. • Amphotericin B, given as a lipid formulation or amphotericin B deoxycholate can be used for initial therapy. After the patient has shown a favorable response, therapy can be changed to itraconazole to complete a total of at least 12 months of therapy. Pulmonary Sporotrichosis • For severe or life-threatening pulmonary sporotrichosis, amphotericin B, given as a lipid formulation, is recommended. Amphotericin B deoxycholate could also be used. • After the patient has shown a favorable response to amphotericin B, therapy can be changed to itraconazole to complete a total of at least 12 months of therapy. • For less severe disease, itraconazole administered for at least 12 months is recommended. • Surgery combined with amphotericin B therapy is recommended for localized pulmonary disease. Meningeal Sporotrichosis • Amphotericin B, given as a lipid formulation for 4–6 weeks, is recommended for the initial treatment of meningeal sporotrichosis. Amphotericin B deoxycholate could also be used but is not preferred. • Itraconazole is recommended as step-down therapy after the patient responds to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of therapy. Disseminated (Systemic) Sporotrichosis • Amphotericin B, given as a lipid formulation, is recommended for disseminated sporotrichosis. Amphotericin B deoxycholate could also be used but is not preferred. • Itraconazole is recommended as step-down therapy after the patient responds to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of therapy. Sporotrichosis in Pregnant Women and in Children • Amphotericin B, given as a lipid formulation, or amphotericin B deoxycholate, is recommended for severe sporotrichosis that must be treated during pregnancy; azoles should be avoided. • For children with disseminated sporotrichosis, amphotericin B should be the initial therapy, followed by itraconazole as step-down therapy.
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[16] (2008)**	Aspergillosis • Voriconazole is the drug of choice but should be used cautiously with HIV protease inhibitors and efavirenz. Amphotericin B deoxycholate or lipid-formulation amphotericin B are alternatives, as is caspofungin and posaconazole. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. Candidiasis (Mucocutaneous) • Oral fluconazole is as effective as topical therapy for oropharyngeal

Clinical Guideline	Recommendation(s)
	candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral solution for 7–14 days is as effective as oral fluconazole but less well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. IV amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used. • Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14–21-day course of either fluconazole (oral or IV) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although IV caspofungin or IV voriconazole are effective in treating esophageal candidiasis among HIV-infected patients, oral or IV fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. <u>Coccidioidomycosis</u> • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped. <u>Cryptococcosis</u> • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the CSF but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a 2-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for 8 weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. <u>Histoplasmosis</u> • Patients with moderately severe to severe disseminated histoplasmosis should be treated with an IV lipid formulation of amphotericin B for

Clinical Guideline	Recommendation(s)
	≥2 weeks or until they clinically improve followed by oral itraconazole. • In patients with less severe disseminated histoplasmosis, oral itraconazole is appropriate initial therapy. Leishmaniasis • Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in HIV-coinfected patients. The optimal amphotericin B dosage has not been determined. • Regimens with efficacy include conventional amphotericin B or liposomal or lipid complex preparations administered on consecutive days or in an interrupted schedule.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer**[17] **(2010)**	Antifungal Therapy in High Risk Patients • Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 4–7 days of antibiotics and whose overall duration of neutropenia is expected to be >7 days. • Data are insufficient to recommend a specific empirical antifungal agent for a patient already receiving antifungal prophylaxis, but switching to a different class of antifungals that is given intravenously should be considered. • Preemptive antifungal management is acceptable as an alternative to empirical antifungal therapy in a subset of high-risk neutropenic patients. Those who remain febrile after 4–7 days of broad-spectrum antibiotics but are clinically stable, have no clinical or chest and sinus computed tomography (CT) signs of fungal infection, have negative serologic assay results for evidence of invasive fungal infection, and have no recovery of fungi from any body site may have antifungal agents withheld. Antifungal therapy should be instituted if any of these indicators of possible invasive fungal infection are identified. • Prophylaxis against *Candida* infection is recommended in patient groups in whom the risk of invasive candidal infection is substantial, such as allogeneic hematopoietic stem cell transplant (HSCT) recipients or those undergoing intensive remission-induction or salvage-induction chemotherapy for acute leukemia. Fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin are all acceptable alternatives. • Prophylaxis against invasive *Aspergillus* infections with posaconazole should be considered for selected patients >13 years of age who are undergoing intensive chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) in whom the risk of invasive aspergillosis without prophylaxis is substantial. Antifungal Therapy Low Risk Patients • In low-risk patients, the risk of invasive fungal infection is low, and therefore routine use of empirical antifungal therapy is not recommended. • Antifungal prophylaxis is not recommended for patients in whom the anticipated duration of neutropenia is >7 days.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the polyenes 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 Polyenes[1-5]

Indication	Amphotericin B	Amphotericin B Cholesteryl Sulfate Complex	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Aspergillosis	✔				
Blastomycosis (North American)	✔				
Candidiasis (systemic)	✔				
Coccidioidomycosis	✔				
Cryptococcosis	✔				
Empirical therapy for presumed fungal infection in febrile, neutropenic patients				✔	
Histoplasmosis	✔				
Leishmaniasis (mucocutaneous)	✔				
Leishmaniasis (visceral)				✔	
Mucormycosis	✔				
Sporotrichosis	✔				
Treatment of cryptococcal meningitis in HIV-infected patients				✔	
Treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy			✔		
Treatment of invasive aspergillosis in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate in effective doses, and in patients with invasive aspergillosis where prior amphotericin B deoxycholate therapy has failed		✔			
Treatment of patients with *Aspergillus* species, *Candida* species and/or *Cryptococcus* species infections refractory to amphotericin B deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate				✔	

Indication	Amphotericin B	Amphotericin B Cholesteryl Sulfate Complex	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Treatment of intestinal and oral cavity infections caused by *Candida albicans*					✔ *
Treatment of candidiasis in the oral cavity					✔ †
Treatment of non-esophageal mucous membrane gastrointestinal candidiasis					✔ ‡
Zygomycosis	✔				

*Powder formulation only
†Suspension formulation only
‡Tablet formulation only

IV. Pharmacokinetics

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

Table 5. Pharmacokinetic Parameters of the Polyenes[1-5]

Generic Name(s)	Protein Binding (%)	Excretion (%)	Half-Life
Amphotericin B	>90	Renal (40)	15 days
Amphotericin B cholesteryl sulfate complex	Not reported	Not reported	28-29 hours
Amphotericin B lipid complex	Not reported	Renal (1)	170 hours
Amphotericin B liposome	Not reported	Renal (10)	7-153 hours
Nystatin	Not reported	Feces	Not reported

V. Drug Interactions

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

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

Generic Name(s)	Significance Level	Interaction	Mechanism
Amphotericin B	1	Digitalis glycosides	Amphotericin B-induced hypokalemia may potentiate digitalis toxicity. Close monitoring of potassium levels and cardiac function 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 polyenes are listed in Table 7. The boxed warning for all amphotericin B products is listed in Table 8. Conventional amphotericin B causes acute infusion-related reactions and nephrotoxicity. Infusion-related reactions include fever, rigors, chills, myalgias, arthralgias, nausea, vomiting, headaches and bronchospasm. The lipid formulations of amphotericin B are associated with a lower risk of nephrotoxicity and infusion-related adverse events than conventional amphotericin B.

Table 7. Adverse Drug Events (%) Reported with the Polyenes[1-5]

Adverse Events	Amphotericin B	Amphotericin B Cholesteryl Sulfate Complex	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Cardiovascular					
Arrhythmias	✔	1 to <5	✔	2-10	-
Atrial fibrillation	-	1 to <5	-	2-10	-
Bradycardia	-	1 to <5	-	2-10	-
Cardiac arrest	✔	-	6	2-10	-
Cardiac failure	✔	-	✔	-	-
Cardiomegaly	-	-	-	2-10	-
Cardiomyopathy	-	-	✔	-	-
Cardiovascular disorder	-	≥5	-	-	-
Chest pain	-	≥5	3	8-12	-
Congestive heart failure	-	1 to <5	-	-	-
Hypertension	✔	7-9	5	8-20	-
Hypotension	✔	9-12	8	7-14	-
Myocardial infarction	-	1 to <5	6	-	-
Orthostatic hypotension	-	≥5	-	2-10	-
Shock	✔	1 to <5	✔	-	-
Supraventricular tachycardia	-	1 to <5	-	-	-
Syncope	-	1 to <5	-	-	-
Tachycardia	-	9-12	-	9-19	✔
Valvular heart disease	-	-	-	2-10	-
Vascular disorder	-	-	-	2-10	-
Vasodilation	-	1 to <5	-	2-10	-
Ventricular extrasystoles	-	1 to <5	-	-	-
Ventricular fibrillation	✔	-	✔	-	-
Central Nervous System					
Agitation	-	1 to <5	-	2-10	-
Anxiety	-	1 to <5	-	7-14	-
Asthenia	-	1 to <5	-	6-8	-
Cerebrovascular accident	-	-	✔	-	-

Adverse Events	Amphotericin B	Amphotericin B Cholesteryl Sulfate Complex	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Coma	-	-	-	2-10	-
Confusion	-	≥5	-	9-13	-
Convulsions	✔	1 to <5	✔	2-10	-
Depression	-	1 to <5	-	2-10	-
Dizziness	-	≥5	-	2-10	-
Dysesthesia	-	-	-	2-10	-
Hallucination	-	1 to <5	-	2-10	-
Headache	✔	4-8	6	9-20	-
Hypertonia	-	1 to <5	-	-	-
Insomnia	-	≥5	-	17	-
Malaise	✔	-	✔	2-10	-
Nervousness	-	1 to <5	-	2-10	-
Neurologic symptoms	✔	-	✔	-	-
Neuropathy	-	1 to <5	-	-	-
Paresthesia	-	1 to <5	-	2-10	-
Peripheral neuropathy	✔	-	✔	-	-
Psychosis	-	1 to <5	-	-	-
Somnolence	-	≥5	-	2-10	-
Speech disorder	-	1 to <5	-	-	-
Stupor	-	1 to <5	-	-	-
Thinking abnormality	-	≥5	-	-	-
Tremor	-	≥5	-	2-10	-
Vertigo	✔	-	✔	2-10	-
Dermatological					
Acne	-	1 to <5	-	-	-
Alopecia	-	1 to <5	-	2-10	-
Dry skin	-	-	-	2-10	-
Ecchymosis	-	1 to <5	-	2-10	-
Erythema	-	-	-	✔	-
Erythema multiforme	-	-	✔	-	-
Exfoliative dermatitis	-	-	✔	-	-
Maculopapular rash	✔	≥5	✔	2-10	-
Petechial rash	-	1 to <5	-	-	-
Pruritus	✔	≥5	✔	11	-
Purpura	-	-	-	2-10	-
Rash	✔	≥5	4	22-25	✔
Skin discoloration	-	1 to <5	-	2-10	-

Adverse Events	Amphotericin B	Amphotericin B Cholesteryl Sulfate Complex	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Skin disorder	-	1 to <5	-	2-10	-
Skin nodule	-	1 to <5	-	-	-
Skin ulceration	-	1 to <5	-	2-10	-
Stevens-Johnson syndrome	✔	-	-	-	✔
Urticaria	-	1 to <5	-	✔	✔
Vesiculobullous rash	-	1 to <5	-	2-10	-
Gastrointestinal					
Abdomen enlarged	-	≥5	-	2-10	-
Abdominal pain	-	≥5	4	10-20	-
Anorexia	✔	1 to <5	✔	2-10	-
Bloody diarrhea	-	1 to <5	-	-	✔
Cholangitis	-	-	✔	-	-
Cholecystitis	-	-	✔	-	-
Constipation	-	1 to <5	-	2-15	-
Cramping	✔	-	✔	-	-
Diarrhea	✔	≥5	6	15-30	✔
Dry mouth	-	≥5	-	2-10	-
Dyspepsia	✔	1 to <5	✔	2-10	-
Dysphagia	-	-	-	2-10	-
Epigastric pain	-	-	✔	-	-
Eructation	-	-	-	2-10	-
Fecal incontinence	-	1 to <5	-	2-10	-
Flatulence	-	-	-	2-10	-
Gastrointestinal disorder	-	1 to <5	-	-	-
Gastrointestinal hemorrhage	-	1 to <5	4	10	-
Gastrointestinal upset	-	-	-	-	✔
Gingivitis	-	1 to <5	-	-	-
Glossitis	-	1 to <5	-	-	-
Gum/oral hemorrhage	-	-	-	2-10	-
Hematemesis	-	≥5	-	2-10	-
Hemorrhagic gastroenteritis	✔	-	-	-	-
Hemorrhoids	-	-	-	2-10	-
Ileus	-	-	-	2-10	-
Melena	✔	1 to <5	✔	-	-
Mouth ulcerations	-	1 to <5	-	-	-
Mucositis	-	-	-	2-10	-
Nausea	✔	7-12	9	26-40	✔

Adverse Events	Amphotericin B	Amphotericin B Cholesteryl Sulfate Complex	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Nausea and vomiting	-	4-11	3	-	-
Oral moniliasis	-	1 to <5	-	-	-
Stomatitis	-	≥5	-	2-10	-
Rectal disorder	-	1 to <5	-	2-10	-
Ulcerative stomatitis	-	-	-	2-10	-
Veno-occlusive liver disease	-	1 to <5	✔	2-10	-
Vomiting	✔	6-11	8	22-32	✔
Weight gain	-	≥5	-	-	-
Weight loss	✔	1 to <5	✔	-	-
Genitourinary					
Acute renal failure	✔	-	-	2-10	-
Albuminuria	-	1 to <5	-	-	-
Angioedema	-	-	-	2-10	-
Anuria	✔	-	✔	-	-
Azotemia	✔	-	-	-	-
Dysuria	-	1 to <5	✔	2-10	-
Glycosuria	-	1 to <5	-	-	-
Hematuria	-	≥5	-	14	-
Hemorrhagic cystitis	-	-	-	✔	-
Hyposthenuria	✔	-	-	-	-
Impotence	-	-	✔	-	-
Kidney failure	-	1 to <5	5	2-10	-
Nephrocalcinosis	✔	-	-	-	-
Oliguria	✔	1 to <5	✔	-	-
Renal function abnormalities	✔	-	-	2-10	-
Renal function decreased	✔	-	✔	-	-
Renal tubular acidosis	✔	-	✔	-	-
Toxic nephropathy	-	-	-	2-10	-
Urinary incontinence	-	1 to <5	-	2-10	-
Urinary retention	-	1 to <5	-	-	-
Urinary tract disorder	-	1 to <5	-	-	-
Vaginal hemorrhage	-	-	-	2-10	-
Hematological					
Agranulocytosis	✔	-	-	✔	-
Anemia	✔	≥5	4	2-48	-
Blood dyscrasias	-	-	✔	-	-
Coagulation defects	✔	≥5	✔	2-10	-

Adverse Events	Amphotericin B	Amphotericin B Cholesteryl Sulfate Complex	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Eosinophilia	✔	-	✔	-	-
Fibrinogen increased	-	1 to <5	-	-	-
Hypochromic anemia	-	1 to <5	-	-	-
Hypoproteinemia	-	1 to <5	-	2-10	-
Leukocytosis	✔	1 to <5	✔	-	-
Leukopenia	✔	1 to <5	4	15-17	-
Petechia	-	1 to <5	-	2-10	-
Prothrombin decreased	-	≥5	-	2-10	-
Prothrombin increased	-	-	-	2-10	-
Thrombocytopenia	✔	1-7	5	2-13	-
Thromboplastin decreased	-	1 to <5	-	-	-
Hepatic					
Acute liver failure	✔	-	✔	-	-
Hepatic failure	-	1 to <5	-	-	-
Hepatitis	✔	-	✔	-	-
Hepatocellular damage	-	-	-	2-10	-
Hepatomegaly	-	-	✔	2-10	-
Jaundice	✔	≥5	✔	-	-
Laboratory Test Abnormalities					
Abnormal liver function tests	✔	4-11	-	7-11	-
Acidosis	✔	1 to <5	✔	2-10	-
Alkaline phosphatase increases	✔	3-7	-	7-22	-
Amylase increased	-	-	-	2-10	-
Bilirubin elevations	✔	2-19	4	11-18	-
Blood urea nitrogen elevations	✔	1 to <5	✔	19-21	-
Creatinine increased	-	12-21	11	19-22	-
GGT increased	✔	1 to <5	-	-	-
Hyperamylasemia	-	-	✔	-	-
Hypercalcemia	-	-	✔	-	-
Hyperchloremia	-	-	-	2-10	-
Hyperglycemia	-	1-6	✔	8-23	-
Hyperkalemia	✔	1 to <5	✔	2-10	-
Hyperlipidemia	-	1 to <5	-	-	-
Hypermagnesemia	-	-	-	2-10	-
Hypernatremia	-	1 to <5	-	4	-
Hyperphosphatemia	-	-	-	2-10	-
Hyperuricemia	-	-	✔	-	-

Adverse Events	Amphotericin B	Amphotericin B Cholesteryl Sulfate Complex	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Hypocalcemia	✔	≥5	✔	5-18	-
Hypoglycemia	-	1 to <5	✔	-	-
Hypokalemia	✔	7-26	5	38-43	-
Hypomagnesemia	✔	4-7	✔	15-26	-
Hyponatremia	-	1 to <5	-	2-12	-
Hypophosphatemia	-	≥5	✔	2-10	-
LDH increased	-	-	-	2-10	-
Liver enzyme elevations	✔	1 to <5	✔	4-15	-
Non-protein nitrogen increased	-	-	-	2-10	-
Serum creatinine elevations	✔	-	-	-	-
Musculoskeletal					
Arthralgia	✔	1 to <5	✔	2-10	-
Back pain	-	≥5	-	12	-
Bone pain	-	-	✔	2-10	-
Dystonia	-	-	-	2-10	-
Myalgia	✔	1 to <5	✔	2-10	✔
Myasthenia	-	-	✔	-	-
Neck pain	-	1 to <5	-	2-10	-
Respiratory					
Apnea	-	≥5	-	-	-
Asthma	-	≥5	✔	2-10	-
Bronchospasm	✔	-	✔	-	✔
Cough increased	-	≥5	-	18	-
Cyanosis	-	-	-	✔	-
Dyspnea	✔	4-9	7	18-23	-
Epistaxis	-	≥5	-	9-15	-
Hemoptysis	-	1 to <5	✔	2-10	-
Hiccup	-	-	-	2-10	-
Hypersensitivity pneumonitis	✔	-	-	-	-
Hyperventilation	-	≥5	-	1-10	-
Hypoventilation	-	-	-	✔	-
Hypoxia	-	5-9	-	6-8	-
Lung disorder	-	≥5	-	14-18	-
Lung edema	-	1 to <5	-	2-10	-
Pharyngitis	-	1 to <5	-	2-10	-
Pleural effusion	-	1 to <5	✔	13	-
Pneumonia	-	-	-	2-10	-

Adverse Events	Amphotericin B	Amphotericin B Cholesteryl Sulfate Complex	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Pulmonary edema	✔	-	✔	✔	-
Pulmonary embolism	-	-	✔	-	-
Respiratory alkalosis	-	-	-	2-10	-
Respiratory disorder	-	1 to <5	4	-	-
Respiratory failure	-	-	8	2-10	-
Respiratory insufficiency	-	-	-	2-10	-
Rhinitis	-	≥5	-	11	-
Sinusitis	-	1 to <5	-	2-10	-
Tachypnea	✔	-	✔	-	-
Wheezing	✔	-	✔	-	-
Special Senses					
Amblyopia	-	1 to <5	-	-	-
Conjunctivitis	-	-	-	2-10	-
Deafness	-	1 to <5	✔	-	-
Diplopia	✔	-	✔	-	-
Dry eyes	-	-	-	2-10	-
Dry nose	-	-	-	2-10	-
Ear disorder	-	1 to <5	-	-	-
Eye hemorrhage	-	≥5	-	2-10	-
Hearing loss	✔	-	✔	-	-
Tinnitus	✔	1 to <5	✔	-	-
Visual impairment	✔	-	✔	-	-
Other					
Accidental injury	-	1 to <5	-	-	-
Allergic reactions	✔	1 to <5	✔	-	-
Anaphylactoid reactions	✔	-	✔	-	-
Angioedema	-	-	-	✔	-
Chills	✔	50-77	18	40-48	-
Death	-	1 to <5	-	-	-
Dehydration	-	1 to <5	-	-	-
Edema	-	≥5	-	12-15	-
Facial edema	-	≥5	-	-	-
Facial swelling	-	-	-	2-10	✔
Fever	✔	33-55	14	7-47	-
Graft versus host disease	-	-	-	2-10	-
Hemorrhage	-	-	-	2-10	-
Herpes simplex	-	-	-	2-10	-

Adverse Events	Amphotericin B	Amphotericin B Cholesteryl Sulfate Complex	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Hypervolemia	-	1 to <5	-	8-12	-
Hypothermia	-	1 to <5	-	-	-
Immune system disorder	-	1 to <5	-	-	-
Infection	-	1 to <5	5	11-13	-
Influenza-like symptoms	-	-	-	2-10	-
Injection site inflammation	-	≥5	✔	2-10	-
Injection site pain	✔	1 to <5	-	-	-
Injection site reaction	✔	1 to <5	✔	-	-
Mucous membrane disorder	-	≥5	-	-	-
Multiple organ failure	-	-	11	-	-
Pain	✔	≥5	5	14	-
Peripheral edema	-	≥5	-	15	-
Phlebitis	✔	1 to <5	-	9-11	-
Procedural complication	-	-	-	2-10	-
Sepsis	-	≥5	7	7-14	-
Shaking	✔	-	-	-	-
Sweating	-	≥5	-	7	-
Thrombophlebitis	✔	-	✔	-	-

✔ Percent not specified
- Event not reported

Table 8. Boxed Warning for Amphotericin B (All Formulations)[1]

WARNING
This drug should be used primarily for treatment of patients with progressive and potentially life-threatening fungal infections; it should not be used to treat noninvasive forms of fungal disease such as oral thrush, vaginal candidiasis, and esophageal candidiasis in patients with normal neutrophil counts. Exercise caution to prevent inadvertent overdose with amphotericin B. Verify the product name and dosage if dose exceeds 1.5 mg/kg.

VII. Dosing and Administration

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

Table 9. Usual Dosing Regimens for the Polyenes[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amphotericin B	Aspergillosis: Total dose up to 3.6 g for a period up to 11 months Life-Threatening Fungal Infections: Initial: 0.25 mg/kg/day IV Maintenance: Depending on the patient's cardio-renal status, doses may gradually be increased by 5 to 10 mg/day to final daily dosage of 0.5 to 0.7 mg/kg The optimal dose is unknown. Total daily dosage may range up to 1 mg/kg/day or up to 1.5 mg/kg when given on alternate days. Rhinocerebral Phycomycosis: Cumulative dose of ≥3 g Sporotrichosis: Total dose up to 2.5 g for a period up to 9 months	Safety and efficacy in children have not been established.	Injection: 50 mg
Amphotericin B cholesteryl sulfate complex	Fungal Infections: 3 to 4 mg/kg IV as required once daily	Fungal Infections: 3 to 4 mg/kg IV as required once daily	Injection: 50 mg 100 mg
Amphotericin B lipid complex	Fungal Infections: 5 mg/kg IV as a single infusion	Fungal Infections: 5 mg/kg IV as a single infusion	Injection: 5 mg/ml
Amphotericin B liposome	Cryptococcal Meningitis in HIV-Infected Patients: 6 mg/kg/day Empirical Therapy: 3 mg/kg/day	Cryptococcal Meningitis in HIV-Infected Patients: 6 mg/kg/day Empirical Therapy: 3 mg/kg/day	Injection: 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Systemic Fungal Infections (*Aspergillus, Candida, Cryptococcus*): 3 to 5 mg/kg/day Visceral Leishmaniasis: Immunocompetent patients: 3 mg/kg/day on days 1-5, and 3 mg/kg/day on days 14 and 21 Immunocompromised patients: 4 mg/kg/day on days 1-5 and 4 mg/kg/day on days 10, 17, 24, 31, and 38	Systemic Fungal Infections (*Aspergillus, Candida, Cryptococcus*): 3 to 5 mg/kg/day Visceral Leishmaniasis: Immunocompetent patients: 3 mg/kg/day on days 1-5, and 3 mg/kg/day on days 14 and 21 Immunocompromised patients: 4 mg/kg/day on days 1-5 and 4 mg/kg/day on days 10, 17, 24, 31, and 38	
Nystatin	Intestinal Candidiasis: Powder: 500,000 to 1 million units 3 times daily Non-Esophageal Mucous Membrane Gastrointestinal Candidiasis: Tablet: 500,000 to 1 million units 3 times daily Oral Cavity Infections (*C. albicans*): Powder/Suspension: 400,000 to 600,000 units 4 times daily	Intestinal Candidiasis: Powder: 500,000 to 1 million units 3 times daily Oral Cavity Infections (*C. albicans*): Infants: Powder/Suspension: 200,000 units 4 times daily Children: Powder/Suspension: 400,000 to 600,000 units 4 times daily	Powder: 50 million units 150 million units 500 million units Suspension: 100,000 units/ml Tablet: 500,000 units

VIII. Effectiveness

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

Table 10. Comparative Clinical Trials with the Polyenes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aspergillosis				
Barnes et al.[18] (1999) Amphotericin B colloidal dispersion (ABCD) 4 mg/kg/day for 12-36 days Oral itraconazole 600 mg/day was initiated as soon as oral therapy could be tolerated.	OL Neutropenic patients with proven or suspected invasive pulmonary aspergillosis	N=12 End of therapy	Primary: Survival at the end of the study period	Primary: Eleven of 12 patients survived the acute episode of neutropenia.
Bowden et al.[19] (2002) Amphotericin B colloidal dispersion (ABCD) 6 mg/kg/day vs amphotericin B deoxycholate (AmB) 1.0-1.5 mg/kg/day	RCT, DB, MC Immuno-compromised patients >2 years of age with newly diagnosed (proven or probable) invasive aspergillosis	N=174 End of therapy	Primary: Therapeutic response Secondary: Overall mortality, death due to fungal infection occurring by study day 84, nephrotoxicity, time to nephrotoxicity	Primary: Rates of therapeutic response were 35 % in both groups (P=0.5). The study was underpowered to detect a difference. Rates of therapeutic response based on complete response, partial response and stable disease were similar between the treatment groups. Secondary: Overall mortality rate was 50% in the ABCD group and 55% in the AmB group. No significant differences were observed. The rate of death due to fungal infection was similar between the groups (P=0.6). Significantly fewer patients discontinued the study medication due to nephrotoxicity in the ABCD group compared to the AmB group (3% and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients were treated for 6 weeks or until 2 weeks after all signs and symptoms of infection disappeared, in addition to resolution of neutropenia.				16% respectively, P=0.001). The drug was discontinued due to overall toxicity in 22% of the patients receiving ABCD and in 24% of the patients receiving AmB. The ABCD group experienced significantly lower nephrotoxicity than in the AmB group (P=0.002). The mean increase in serum creatinine levels was significantly less in the ABCD group than in the AmB group (P=0.05). The median time to nephrotoxicity was 22 days in the AmB group and 301 days in the ABCD group (P<0.001).
White et al.[20] (1997) Amphotericin B colloidal dispersion (ABCD) 2-8 mg/kg/day vs amphotericin B deoxycholate 0.1-1.4 mg/kg/day	RETRO Patients with aspergillosis treated with amphotericin B or ABCD at 6 cancer or transplant centers	N=343 120 days	Primary: Therapeutic response, development of renal toxicity, mortality rates	Primary: Complete or partial response was seen in 48.8% of ABCD patients and 23.4% of amphotericin B patients (P<0.001). Overall, 50% of patients in the ABCD group died compared to 71.6% of patients in the amphotericin B group (P<0.001). Renal toxicity developed in 43.1% of patients in the amphotericin B group compared to 8.2% in the ABCD group (P<0.001). Renal toxicity occurred significantly earlier in the amphotericin B group compared to the ABCD group (P<0.001).
Herbrecht et al.[21] (2002) Amphotericin B deoxycholate 1.0-1.5 mg/kg/day vs voriconazole	RCT, DB, MC Immuno-compromised patients ≥12 years of age with definite or probable invasive aspergillosis	N=277 12 weeks	Primary: Clinical response Secondary: Response at end of initial therapy, safety outcomes, survival up to week 12	Primary: Successful response at week 12 in patients receiving voriconazole and amphotericin B deoxycholate was 52.8% and 31.6%, respectively and was significantly better in the voriconazole group. Secondary: Successful response at end of initial therapy in patients receiving voriconazole and amphotericin B deoxycholate was 49.7% and 27.8%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
6 mg/kg IV 2 times daily on day 1, 4 mg/kg IV 2 times daily for ≥7 days, then 200 mg orally 2 times daily				There were significantly fewer adverse events in the voriconazole group compared to the amphotericin B group (P=0.02). Visual disturbances (44.8% vs 4.3%, P<0.001), chills and/or fever (3.1% vs 24.9%, P<0.001) and severe adverse events (13.4% vs 24.3%, P=0.008), including renal impairment (1.0% vs 10.3%, P<0.001), hypokalemia (0% vs 3.2%, P=0.01) and systemic events (0.5% vs 3.8%, P=0.03) occurred in patients receiving voriconazole and amphotericin B deoxycholate, respectively. The survival rate for patients receiving voriconazole and amphotericin B deoxycholate was 70.8% and 57.9%, respectively.
Wingard et al.[63] (2007) Amphotericin B deoxycholate 1.0-1.5 mg/kg/day (CAB) vs voriconazole 6 mg/kg IV 2 times daily on day 1, 4 mg/kg IV 2 times daily for ≥7 days, then 200 mg orally 2 times daily	RCT, DB, MC (Post-hoc analysis) Immuno-compromised patients ≥12 years of age with definite or probable invasive aspergillosis	N=277 12 weeks	Primary: Resource utilization	Primary: In the overall clinical trial population, total hospital days and ICU days were similar for the voriconazole and CAB groups (total: 27.82 vs 27.71, P=0.97; and ICU: 5.59 vs 8.07, P=0.11). For survivors, voriconazole treatment was associated with a similar number of total hospital days (29.83 vs 32.01 days, P=0.54) compared with CAB, but significantly fewer ICU days (3.86 vs 8.21, P=0.03). For non-survivors, those treated with voriconazole had a similar number of total (22.96 vs 21.77, P=0.73) and ICU (9.76 vs 7.87, P=0.44) days in the hospital. Similar patterns of resource use across the treatment groups were observed for outpatient visits, specialist visits, and general practice physician visits. In the total population, days of IV therapy were fewer for voriconazole than for CAB (20.9 vs 30.0, P<0.01) and days of oral therapy were greater in the voriconazole arm (45.4 vs 16.5, P<0.01). For survivors, patients in the voriconazole treatment arm had fewer days on intravenous therapy than those in the CAB group (21.9 vs 38.9 days, P<0.01) but more days on oral therapy than CAB (58.8 vs 25.7, P<0.01). For non-survivors, the number of days on intravenous therapy was similar for voriconazole and CAB (18.3 vs 17.7 days, P=0.81) and higher for voriconazole for oral therapy (13.3 vs 3.9, P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients in the voriconazole group had significantly more hospital-free survival days than those in the CAB group (P<0.001).
Caillot et al.[71] (2007) Amphotericin B liposome 10 mg/kg per day vs caspofungin 70 mg on day 1, followed by 50 mg daily thereafter plus amphotericin B liposome 3 mg/kg per day	RCT, MC Immuno-compromised patients ≥10 years of age with proven or probable invasive aspergillosis	N=30 12 week posttreatment follow-up	Primary: Percentage of patients who had favorable overall responses (partial or complete responses) at the end of therapy (EOT). Secondary: Time to favorable overall response, time to complete response, survival at EOT, percentage of patients with recurrent infection (defined as failure for overall response), and survival during the 4-week posttreatment follow-up	Primary: The overall response at EOT was significantly more favorable for patients in the combination group (67%) compared with patients in the high-dose monotherapy group (27%; P=0.028). Secondary: At week 12, a favorable response was obtained by 10 of 15 patients in the high-dose monotherapy group (67%; 8 patients had a partial response and 2 patients had a complete response) and by 12 of 15 patients in the combination group (80%; 9 patients had a partial response and 3 patients had a complete response). A favorable or unfavorable response at EOT was independent of hematologic status at EOT (recurrence, remission, or stable; P=0.442). The survival rate at EOT was 97% (1 death had occurred in the high-dose monotherapy group). At week 12, all 15 patients in the combination group were alive, whereas 3 of 15 patients had died in the high-dose monotherapy group. Those 3 patients died due to progression of the underlying hematologic condition; and, in 1 patient, fungal infection contributed to the death. Study drug-related adverse events were less frequent in the combination group than in the high-dose monotherapy group.
Cornely et al.[64] (2007) Amphotericin B liposome 3 mg/kg/day for 14 days (standard dose arm) vs	RCT, DB Patients with a diagnosis of proven or probable invasive aspergillosis and other mold infections	N=339 1-60 days	Primary: Overall response (clinical, radiological, microbiological findings) at the end of the study drug treatment Secondary:	Primary: There was no significant difference with regards to favorable overall responses between the treatment groups (50% in the standard-dose group vs 46% in the high-dose group; P=0.65). Secondary: The rate of survival at the end of study drug treatment was 93% in the standard-dose group and 88% in the high-dose group (95% CI, -4% to 12%; P>0.05). At 12 weeks after study entry, the survival rates were 72% and 59% for the standard- and high-dose groups, respectively (95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amphotericin B liposome 10 mg/kg/day for 14 days (high dose arm) After 14 days of treatment, all patients received the open-label drug at a dosage of 3 mg/kg/day			Survival (up to 12 weeks) and adverse events	-0.2% to 26%; P>0.05). Nephrotoxicity occurred at a greater rate in the high-dose group (31% vs 14%; P<0.01). Grade 3 hypokalemia (blood potassium level, <3.0 mmol/L) was also more frequently found in the high-dose group (30% vs 16%; P=0.015). There was no difference between the groups with regard to the rates of grade 4 hypokalemia (blood potassium level, <2.5 mmol/L). No differences in the rates of drug-related reactions, including hypersensitivity/anaphylaxis, chills, or hypotension, were reported. There was a difference in the rates of study drug discontinuation resulting from adverse events (20% in the standard-dose group and 32% in the high-dose group; P=0.035). The most common events leading to study drug discontinuations in both groups were increases in the creatinine level, abnormal liver test results, and hypokalemia.
Raad et al.[66] (2008) Amphotericin B liposome 7.5 mg/kg/day (L-AMB) vs amphotericin B liposome 7.5 mg/kg/day plus caspofungin 70 mg on day 1, followed by 50–100 mg daily vs posaconazole 800 mg orally in	RCT Patients with hematologic malignancies and invasive aspergillosis enrolled in a compassionate-use trial of antifungal salvage therapy	N=143 Up to 12 weeks	Primary: Response rate to salvage therapy Secondary: Deaths related to aspergillosis within 12 months after initiation of salvage therapy and adverse events	Primary: The overall response rate to salvage therapy was 40% for posaconazole, 8% for L-AMB ($P \leq 0.001$) and 11% for combination therapy ($P < 0.002$). Secondary: Aspergillosis contributed to the death of 40% of posaconazole group, 65% of the L-AMB group and 68% of the combination group ($P \leq 0.008$). By multivariate analysis, posaconazole therapy independently improved response (95% CI, 2.8–32.5; P<0.001). L-AMB alone or in combination with caspofungin was associated with a significantly higher rate of nephrotoxicity (P≤0.02) and hepatotoxicity ($P < 0.03$) than monotherapy with posaconazole.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
divided doses daily				
Candidiasis (Oropharyngeal/Esophageal)				
Villanueva et al.[76] (2001) Amphotericin B 0.5 mg/kg/day for 14 days vs caspofungin 50 mg for 14 days vs caspofungin 70 mg for 14 days	RCT, DB, MC Patients 21-65 years of age with endoscopically and microbiologically documented *Candida* esophagitis	N=128 28 days	Primary: Combined clinical and endoscopic response and microbiological response	Primary: The highest response rate was observed in the caspofungin 70 mg group and the lowest was observed in the amphotericin B group. The mean differences in response rates for caspofungin versus amphotericin B were 11% (95% CI, -9% to 32%) and 26% (95% CI, 4%–50%) for those receiving 50 and 70 mg, respectively, at the primary end point 2 weeks after discontinuation of therapy. Analysis of all evaluable patients (per protocol) were similar to the modified intention-to-treat analysis for combined response rates: 88%, 96%, and 78% at the end of therapy and 77%, 89%, and 68% 2 weeks after discontinuation of therapy for patients receiving caspofungin 50 mg, caspofungin 70 mg and amphotericin B, respectively. Time to resolution of symptoms was not different for any of the treatment groups. More than half the patients in each treatment arm had resolution of all symptoms by day 4 of therapy. Symptoms persisted in 7%, 0%, and 13% of patients at the end of therapy in the groups receiving caspofungin 50 mg, caspofungin 70 mg and amphotericin B, respectively. Endoscopic improvement was slightly higher in the caspofungin groups compared to the amphotericin B groups. Marked reduction in endoscopic grade was observed in 74%, 89%, and 63% of patients in the caspofungin 50 mg group, 70 mg group and amphotericin B group, respectively. Caspofungin had slightly higher fungal eradication rates compared to amphotericin B. *C albicans* was not isolated from 71%, 85%, and 60% of patients taking caspofungin 50 mg, 70 mg, and amphotericin B, respectively. Eradication rates for non-*albicans* species were 64%, 71%, and 40% for caspofungin 50 mg, 70 mg, and amphotericin B, respectively.
Arathoon et al.[75]	RCT, DB, DR	N=140	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Amphotericin B 0.5 mg/kg/day for 7-14 days vs caspofungin 35 mg, 50 mg, or 70 mg daily for 7-14 days	Patients 18-65 years of age with a diagnosis of oropharyngeal and/or esophageal candidiasis	10-18 days	Clinical response Secondary: Microbiological eradication	A higher portion of patients in the caspofungin groups achieved a favorable clinical response (74% to 91%) compared to the amphotericin B treatment group (63%), however this was not statistically significant. More patients with oropharyngeal disease had a favorable response (85%) compared to those with esophageal involvement (73%). Secondary: Microbiological eradication was observed in a larger portion of patients in the caspofungin groups compared to the amphotericin B group. There was no significant difference in the clearance of *C albicans* versus non-*albicans* species.
Kartsonis et al.[58] (2002) Amphotericin B 0.5 mg/kg/day vs caspofungin 35 mg, 50 mg, or 70 mg daily vs fluconazole 200 mg IV daily	RETRO Symptomatic patients with endoscopically confirmed *Candida* esophagitis and decreased susceptibility to fluconazole	N=32 3-14 days posttreatment follow-up	Primary: Clinical outcomes	Primary: Favorable response was seen in 64% of patients with infections which were clinically refractory to fluconazole and subsequently treated with amphotericin B. Favorable response to caspofungin was seen in 79% of patients with infections that had decreased susceptibility to fluconazole.
Flynn et al.[52] (1995) Nystatin 400,000 units 4 times daily for 14 days (swish and swallow)	RCT, MC, SB Children 5 months to 14 years of age with oral thrush	N=182 42 days	Primary: Clinical and microbiologic response	Primary: Significantly more patients treated with fluconazole were clinically cured (78% and 37% respectively, P<0.001). Significantly more patients treated with fluconazole experienced mycological eradication (55% and 6% respectively, P<0.001). At the end of therapy, significantly more patients taking the higher dose of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluconazole suspension 4 mg/kg loading dose followed by 2 mg/kg daily for 14 days The dose of fluconazole was increased halfway through the study to 6 mg/kg loading dose followed by 3 mg/kg daily.				fluconazole had mycological eradication compared to the lower dose (P<0.01).
Goins et al.[53] (2002) Nystatin 100,000 units 4 times daily (applied with soaked cotton or washcloth) for 10 days vs fluconazole suspension 3 mg/kg/day for 7 days	OL, PRO, RCT Infants 1-12 months of age with signs of oral thrush	N=34 28 days	Primary: Clinical and microbiologic response	Primary: At the end of therapy, 28.6% of nystatin patients and 100% of fluconazole patients were clinically cured (P<0.0001). At the end of therapy, 5.6% of nystatin patients and 73.3% of fluconazole patients were microbiologically cured (P<0.0001). By day 28, 23% of fluconazole patients had evidence of clinical relapse (relapse not evaluated in nystatin group).
Pons et al.[54] (1997) Nystatin 500,000 units four times	RCT, MC, PRO Patients with AIDS or HIV and typical signs and symptoms	N=167 42 days	Primary: Clinical and mycological response	Primary: Significantly more patients in the fluconazole group were considered clinically cured compared to patients in the nystatin group (87% and 52% respectively, P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for 14 days (swish and swallow) vs fluconazole suspension 100 mg once daily (after 200-mg loading dose) for 14 days	of oropharyngeal candidiasis			Significantly more patients in the fluconazole group experienced mycological eradication compared to the nystatin group (60% and 6% respectively, P<0.001).
Blomgren et al.[55] (1998) Nystatin rinse with 1 mL for 5 minutes 4 times daily for 3 weeks vs fluconazole 50 mg orally daily for 7 days	RCT Patients with a diagnosis of oral candidiasis	N=71 6 month posttreatment follow-up	Primary: Clinical response	Primary: No significant differences were observed between groups in clinical response.
Candidiasis (Systemic)				
Mora-Duarte et al.[23] (2002) Amphotericin B 0.6-0.7 mg/kg/day (non-neutropenic patients) or 0.7-1.0 mg/kg/day (neutropenic patients)	RCT, DB, DD Patients 18 years of age and older with one or more positive *Candida* cultures in the previous 4 days	N=239 8 weeks posttreatment follow-up	Primary: Overall response to treatment at the end of IV therapy	Primary: At the end of IV therapy, favorable response was observed in 73.4% of patients in the caspofungin group and 61.7% in the amphotericin B group. After adjusting for neutropenic status, the difference in percentage with a favorable response was 12.7% (P=0.09). Among patients meeting the prespecified criteria for evaluation, 80.7% of caspofungin patients and 64.9% of amphotericin B patients had a favorable response (P=0.03). A larger portion of patients in the amphotericin B group had toxicities requiring a change in therapy compared to the caspofungin group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs caspofungin 70 mg loading dose then 50 mg daily After 10 days of IV therapy, non-neutropenic patients could be switched to oral fluconazole 400 mg daily if appropriate.				(P=0.03).
DiNubile et al.[70] (2005) Amphotericin B 0.6-1.0 mg/kg/day vs caspofungin 70 mg loading dose followed by 50 mg daily thereafter All patients could be switched to oral fluconazole therapy after 10 days of IV therapy.	RETRO Adult patients with proven invasive candidiasis	N=239 14 days following last positive culture	Primary: Clinical outcomes	Primary: Favorable responses were slightly lower in patients with cancer compared to those without cancer (62% and 70%, respectively). Favorable responses were seen in 61% of caspofungin patients and 50% of amphotericin B patients with hematological malignancies, and in 80% and 59%, respectively, in patients with solid organ malignancies. Of patients who were neutropenic at baseline, 46% responded favorably to treatment compared to 70% of non-neutropenic patients. Of neutropenic patients, 50% in the caspofungin group responded favorably compared to 40% in the amphotericin B group. The response rate for non-*albicans Candida* species was 76% compared to 48% for *albicans* species. Favorable response rates for *C albicans* and *C tropicalis* infections were 56% and 71%, respectively, in the caspofungin group and 45% and 43%, respectively, in the amphotericin B group.
Anaissie et al.[25] (1996)	RCT, MC, PRO Patients 13 years of	N=164 End of therapy	Primary: Response rates, survival rates,	Primary: Overall response rates were not significantly different between the treatment groups (P>0.26).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amphotericin B 25-50 mg daily (non-neutropenic patients) or 0.67 mg/kg/day (neutropenic patients) vs fluconazole 400 mg daily IV for 5 days then orally thereafter	age and older with documented or presumed fungal infections		adverse events	Median time to defervescence was 5 days in both groups. Median duration of therapy was not statistically different between groups (P=0.80). There were no significant differences in survival rates between groups The incidence of adverse events was significantly higher in the amphotericin B group compared to the fluconazole group (P<0.0001).
Phillips et al.[26] (1997) Amphotericin B 0.6 mg/kg/day vs fluconazole 800 mg IV loading dose on day 1 then 400 mg IV daily for 4 weeks Patients could be switched to oral fluconazole after 10 days of IV therapy if fungemia had cleared and patients could tolerate oral	CS, RCT, SB Patients 18 years of age and older with one or more blood cultures positive for a yeast species	N=106 6 months	Primary: Clinical response	Primary: Successful response was seen in 50% of fluconazole patients and 58% of amphotericin B patients (P=0.39). Therapy failed in 1 amphotericin B patient during the 6th month of follow-up.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
medication.				
Rex et al.[27] (1994) Amphotericin B 0.5-0.6 mg/kg/day IV for the first 7 days then 3 times per week vs fluconazole 400 mg daily IV for 7 days then orally (or at 6 mg/kg if >90 kg or <50 kg)	MC, RCT Patients 13 years of age and older with at least 1 positive blood culture for *Candida* species	N=237 12 week posttreatment follow-up	Primary: Response rates Secondary: Response rates in the intent-to-treat population, outcome in patients who received at least 5 days of therapy	Primary: No significant difference was observed between fluconazole and amphotericin B in successful response to therapy (70% and 79% respectively, P=0.22). Secondary: No significant difference was observed in the intent-to-treat population between fluconazole and amphotericin B in successful response to therapy (72% and 80% respectively, P=0.17). In patients who had received at least 5 days of treatment, 75% of fluconazole patients and 86% of amphotericin B patients had a successful outcome (P=0.05).
Kulberg et al.[28] (2005) Amphotericin B 0.7-1.0 mg/kg/day vs voriconazole 6 mg/kg IV every 12 hours for 1 day then 3 mg/kg every 12 hours Patients could be switched to oral voriconazole after 3 days, and patients in the amphotericin	RCT, MC Patients 12 years of age and older with candidemia	N=370 12 week posttreatment follow-up	Primary: Response to treatment Secondary: Time to first negative blood culture, time from randomization to death	Primary: No significant difference between groups was observed in successful response to treatment (P=0.96). Significantly more patients in the voriconazole group infected with *C. tropicalis* were considered to have a successful response compared to the amphotericin group (32% and 6% respectively, P=0.032). Secondary: No significant difference between groups was observed in the time to first negative blood culture (2 days in each group). No significant difference between groups was observed in the time from randomization to death (36% in the voriconazole group died in the first 14 days compared to 42% in the amphotericin B group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
group were switched to IV or oral fluconazole after a minimum of 3 days.				
Abele-Horn et al.[22] (1996) Amphotericin B 1-1.5 mg/kg/day every other day plus flucytosine 3×2.5 g as a total daily dose vs fluconazole 400 mg on day 1 then 200 mg daily IV	RCT, MC, PRO Patients 18-80 years of age in the intensive care unit (ICU) with evidence of systemic *Candida* infections	N=72 14 days	Primary: Clinical and microbiological response	Primary: No significant differences were seen between the treatment groups in the treatment of pneumonia and sepsis/fungemia. In the treatment of peritonitis, amphotericin B plus flucytosine was more effective than fluconazole, as seen in clinical and microbiological response (P<0.05).
Kujath et al.[24] (1993) Amphotericin B 0.5 mg/kg/day plus flucytosine 3×2.5 g as a total daily dose vs fluconazole 400 mg on day 1 then 300 mg daily IV	OL, PRO, RCT Patients 18 years of age and older with systemic candidiasis	N=40 Variable duration	Primary: Microbiological response, time to elimination of all fungi	Primary: No statistical difference was observed between groups in microbiological elimination or improvement (P=0.44). Fungal elimination was observed significantly sooner in the amphotericin B plus flucytosine group compared to the fluconazole group (5.5 days and 8.5 days respectively, P=0.03).
Queiroz-Telles et al.[72] (2008)	RCT, DB Pediatric patients	N=106 12-week	Primary: Response rate based on the	Primary: In the modified intent-to-treat (MITT) population, the rate of overall treatment success was similar for micafungin (72.9%) compared with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amphotericin B liposome 3 mg/kg/day vs micafungin 2 mg/kg/day (≤40 kg) or 100 mg/day (>40 kg)	<16 years old with clinical signs of systemic *Candida* infection and one or more positive *Candida* cultures from blood or another sterile site within the previous 4 days	posttreatment follow-up	assessment of overall treatment success (clinical and mycological response at the end of therapy)	liposomal amphotericin B (76%; 95% CI, -20.1 to 15.3). Consistent findings were observed for the per protocol population, which showed success rates of 85.4% and 88.1% in the micafungin and liposomal amphotericin B groups, respectively (95% CI, -16.4 to 12.7). Mycologic persistence at the end of therapy was observed for 15.6% patients in both the micafungin and liposomal amphotericin B groups in the MITT population. Three patients in the micafungin group and none in the liposomal amphotericin B group had a proven recurrent fungal infection during the posttreatment phase. The mortality rate during the treatment phase was 1.9% for micafungin and 11.1% for liposomal amphotericin B in the ITT population. During the entire study, including the 12-week follow-up, the mortality rates were 25.0% and 24.1% of patients, respectively. The fungal infection was considered by the investigator to have contributed to the cause of death for 7.7% and 5.6% of patients, respectively. The incidence of adverse events was similar between the treatment groups.
Kuse et al.[73] (2007) Amphotericin B liposome 3 mg/kg/day vs micafungin 2 mg/kg/day (≤40 kg) or 100 mg/day (>40 kg)	RCT, DB Patients ≥16 years old with clinical signs of systemic *Candida* infection and one or more positive *Candida* cultures from blood or another sterile site within the previous 4 days	N=531 12-week posttreatment follow-up	Primary: Response rate based on the assessment of overall treatment success (clinical and mycological response at the end of therapy)	Primary: In the modified intention-to-treat population (MITT), 74.1% of patients were treated successfully with micafungin versus 69.6% of those treated with lipo somal amphotericin B (95% CI, –3.0 to 12.8). In the intention-to-treat population (ITT), success rates were 71.6% with micafungin and 68.2% with liposomal amphotericin B 95% CI, -3.9 to 11.6). In the per-protocol population, treatment success rates were 81.4% for micafungin and 80.4% for liposomal amphotericin B (95% CI, -6.1 to 9.6). Mycological persistence at the end of therapy was observed in 9% of patients in the micafungin group and 9% of patients in the liposomal amphotericin B group in the per-protocol population. Species specificity for mycological persistence was similar between treatment groups. A recurrent *Candida* infection during the 12-week posttreatment period was seen in 7 patients who had received micafungin and 6 patients who had received liposomal amphotericin B.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In the ITT population, 18% of patients died in the micafungin group and 17% of patients died in the liposomal amphotericin B group during the treatment phase. During the study, including the 12-week follow-up period, 40% of patients in the micafungin group and 40% of patients in the liposomal amphotericin B group died. The fungal infection was considered by the investigator to have contributed to the cause of death for 13% patients in the micafungin group and 9% patients in the liposomal amphotericin B group (P=0.22). There were fewer treatment-related adverse events in the micafungin group than in the liposomal amphotericin B group. There were fewer cases of hypokalemia, rigors, increased serum creatinine, and back pain in the micafungin group than in the liposomal amphotericin B group, as well as fewer infusion-related reactions.
Gafter-Gvili et al.[74] (2008) <u>Group 1</u> Echinocandins vs other antifungal agents <u>Group 2</u> Fluconazole vs other antifungal agents	MA Trials that included patients with confirmed invasive candidiasis	N=3,265 (15 trials) Variable duration	Primary: 30-day all-cause mortality Secondary: Treatment failure, microbiological failure, adverse events	Primary: <u>Fluconazole vs other antifungal agents (9 studies)</u> No difference in mortality was observed with fluconazole vs amphotericin B (RR, 0.92; 95% CI, 0.72-1.17). No difference in mortality was observed between fluconazole and itraconazole (RR, 1.91; 95% CI, 0.39-9.35) or between fluconazole and a combination of fluconazole and amphotericin B (RR, 0.98; 95% CI, 0.70-1.35). <u>Echinocandins vs other antifungal agents (4 studies)</u> There was no difference in mortality with anidulafungin vs fluconazole (RR, 0.73; 95% CI, 0.48-1.10). There was no difference in mortality with caspofungin vs amphotericin B (RR, 1.08; 95% CI, 0.75-1.55) or with micafungin vs liposomal amphotericin B (RR, 1.04; 95% CI, 0.75-1.43). <u>Other comparisons (2 studies)</u> There was no difference in mortality with micafungin vs caspofungin (100 mg/d: RR, 1.10; 95% CI, 0.80-1.51; 150 mg/d: RR, 1.27; 95% CI, 0.93-1.72).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no difference in mortality with amphotericin B plus fluconazole vs voriconazole (RR, 1.18; 95% CI, 0.90-1.54). Secondary: <u>Fluconazole vs other antifungal agents (9 studies)</u> No significant difference in treatment failure was found with fluconazole and amphotericin B (RR 1.22; 95% CI, 0.97-1.54) or with fluconazole vs a combination of fluconazole and amphotericin B (RR 1.41; 95% CI, 0.99-1.99). Microbiological failure was higher in patients treated with fluconazole compared to amphotericin B (RR 1.52; 95% CI, 1.12-2.07) or with fluconazole vs a combination of fluconazole and amphotericin B (RR 2.69; 95% CI, 1.17-6.18). No difference in adverse events requiring discontinuation was noted with fluconazole vs amphotericin B (RR 0.45; 95% CI, 0.13-1.56), itraconazole (RR 0.32; 95% CI, 0.04-2.82) or with fluconazole vs a combination of fluconazole and amphotericin B (RR 1.16; 95% CI, 0.49-2.75). Fluconazole caused less nephrotoxicity than amphotericin B (RR, 0.11; 95% CI, 0.03-0.48) or the combination of amphotericin B and fluconazole (RR, 0.12; 95% CI, 0.04-0.39). <u>Echinocandins vs other antifungal agents (4 studies)</u> Treatment failure significantly decreased with anidulafungin vs fluconazole (RR, 0.61; 95% CI, 0.42-0.89). There was no difference in treatment failure with caspofungin vs amphotericin B (RR, 0.70; 95% CI, 0.47-1.03) or with micafungin vs liposomal amphotericin B (RR, 0.93; 95% CI, 0.74-1.19). Microbiological failure was significantly reduced with anidulafungin vs fluconazole (RR, 0.50; 95% CI, 0.29-0.86). No difference in microbiological failure was noted for caspofungin vs amphotericin B (RR, 0.95; 95% CI, 0.40-2.25) or with micafungin vs liposomal amphotericin B (RR, 1.01; 95% CI, 0.53-1.92). A significant decrease in adverse events requiring discontinuation was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				observed with anidulafungin vs fluconazole (RR, 0.52; 95% CI, 0.29-0.92). Caspofungin was associated with a significantly lower rate of adverse events requiring discontinuation when compared with amphotericin B (RR, 0.11; 95% CI, 0.04-0.36) or liposomal amphotericin B (RR, 0.45; 95% CI, 0.26-0.80). <u>Other comparisons (2 studies)</u> There was no difference in treatment failure with micafungin and caspofungin (100 mg/d: RR, 0.85; 95% CI, 0.60-1.20; 150 mg/d: RR, 1.04; 95% CI, 0.74-1.42). There was no difference in treatment failure with amphotericin B plus fluconazole vs voriconazole (RR, 1.00; 95% CI, 0.83-1.19). There was no difference in microbiological failure with micafungin and caspofungin (100 mg/d: RR, 0.73; 95% CI, 0.41-1.22; 150 mg/d: RR, 1.10; 95% CI, 0.70-1.73). There was no difference in adverse events requiring discontinuation with micafungin and caspofungin. Adverse events requiring discontinuation were significantly lower (RR, 0.47; 95% CI, 0.23-0.93) and nephrotoxicity was significantly higher (RR, 2.64; 95% CI, 1.57-4.44) with the amphotericin B-fluconazole arm compared to voriconazole.
Cryptococcal Meningitis				
Leenders et al.[33] (1997) Amphotericin B deoxycholate 0.7 mg/kg/day for 3 weeks (AMB-d) vs amphotericin B liposome 4 mg/kg/day for 3 weeks (L-AMB)	RCT Hospitalized HIV-infected patients ≥18 years of age with a primary episode of cryptococcal meningitis	N=28 6 months posttreatment follow-up	Primary: Clinical response, mycological response, time to mycological response	Primary: Clinical response rates after the first 3 weeks of treatment were 80% in the L-AMB group and 86% in the AMB-d group (P=1.0). The median time to clinical response was 15 days in both treatment groups. During the 7 weeks of fluconazole treatment, 1 L-AMB patient died, and 2 patients in the AMB-d group died. At week 10, clinical response was observed in 87% of the L-AMB group and in 83% of the AMB-d group. No relapses were recorded during the 10 week study period or the 6 month follow-up.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Both treatments were followed by 7 weeks of fluconazole 400 mg daily.				CSF culture conversion was observed in 6 of 15 L-AMB patients compared to 1 of 12 AMB-d patients within the first 7 days of treatment (P=0.09). CSF culture conversion was observed in significantly more L-AMB patients compared to AMB-d patients within the first 14 days of treatment (P=0.01). CSF culture conversion was observed in 11 of 15 L-AMB patients compared to 3 of 8 AMB-d patients within the first 21 days of treatment (P=0.18). Time to CSF culture conversion was significantly shorter in the L-AMB group compared to the AMB-d group (P<0.05) according to Kaplan-Meier estimates.
Techapornroong et al.[67] (2007) Amphotericin B deoxycholate 1 mg/kg once daily for 14 days (OD group) vs amphotericin B deoxycholate 2 mg/kg every other day for 14 days (AD group) After completion of the intensive phase, patients with a successful response were given fluconazole (400 mg/d). Patients without a successful response continued	RCT, DB HIV-infected patients ≥15 years old with cryptococcal meningitis	N=28 ≥3 months	Primary: Clinical outcomes, mycological outcomes, adverse events	Primary: A clinical response was observed in 12 of 15 (80%) patients and 10 of 13 (76.9%) patients in the OD and AD groups, respectively (P=1.0). A mycological response was observed in 3 of 9 (33.3%) patients and 1 of 10 (10%) patients in the OD and AD groups, respectively (P=0.3). At 3 months of treatment, there were 9 and 12 patients in the OD and AD groups, respectively, for analysis. Nine of 21 (43%) patients (5 and 4 in the OD and AD groups, respectively) had clinically relapsed. All 9 patients had evidence of increased ICP, and 5 underwent continuous CSF drainage (2 with lumbar drainage, 1 with ventriculostomy, 1 with lumboperitoneal shunt, and 1 with ventriculoperitoneal shunt). All 21 and 5 of 9 patients had positive CSF cryptococcal antigen and culture for C. neoformans, respectively. Four patients (1 and 3 in the OD and AD groups, respectively) died due to no control of increased ICP including brain herniation, cerebral anoxia; 1 patient died due to bacterial sepsis. At 2 weeks of treatment, the median and mean creatinine levels as well as the percentage of patients with increased creatinine levels from the baseline levels between the 2 groups were not significantly different. Two (13.3%) and 5 (38.5%) patients in the OD and AD groups, respectively, had creatinine levels that were 2 times more than the baseline levels at 2 weeks of treatment (P=0.46). The percentage of patients who had anemia, hypokalemia, or hypomagnesaemia did not differ significantly between the 2 groups (P=1.0). Neutropenia was more commonly observed in the OD group than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amphotericin B treatment.				in the AD group (P=0.08). There was no difference in the incidence of infusion-related events between the 2 groups.
Hamill et al.[6] (2010) Amphotericin B deoxycholate (AMB-d) 0.7 mg/kg/day for 11-21 days vs amphotericin B liposome (L-AMB 3) 3 mg/kg/day for 11-21 days vs amphotericin B liposome (L-AMB 6) 6 mg/kg/day for 11-21 days At the end of induction, all patients received fluconazole 400 mg QD to complete 10 weeks of acute therapy.	MC, DB, RCT Patients with AIDS and acute cryptococcal meningitis	N=267 10 weeks	Primary: Incidence of mycological success (conversion of CSF culture results) at week 2 Secondary: Survival at week 10 among and adverse events	Primary: CSF culture results were negative at week 2 in 47.5% of patients who received AMB-d, in 58.3% of those who received L-AMB 3, and in 48.0% of those who received L-AMB 6. None of these differences among the groups were statistically significant (treatment difference for L-AMB 3 vs AMB-d, 10.8% [95% CI, -6.9% to 28.5%]; treatment difference for L-AMB 6 vs AMB-d, 0.5% [95% CI, -16.4% to 17.3%]). Secondary: Overall mortality at week 10 was 11.6%, with no significant differences among the treatment groups. The overall incidence of infusion–related reactions was significantly lower for both the 3 mg/kg/day and 6 mg/kg/day dosages of liposomal amphotericin B, compared with conventional amphotericin B (P<.001). Significantly fewer patients who received the 3 mg/kg/day dosage of liposomal amphotericin B developed nephrotoxicity, indicated by a doubling of the serum creatinine value, compared with recipients of conventional amphotericin B (P=.004).
de Lalla et al.[35]	OL	N=31	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1995) Amphotericin B 1 mg/kg/day for 14 days Some patients also received flucytosine 100-150 mg/kg in 4 doses IV or orally. At the end of primary therapy, patients received either itraconazole or fluconazole for suppressive therapy.	Patients with AIDS and either cryptococcal meningitis (CM) or extrameningeal disseminated cryptococcosis	2 months	Therapeutic response (success= resolution of symptoms and negative CSF cultures plus a fall in cryptococcal antigen titer after 2 months of therapy; favorable= clinical improvement and negative blood culture plus a decrease in antigen titer after 2 months of therapy)	Therapeutic success was observed in 93.5% of all cases. Nephrotoxicity developed in 7 cases, requiring discontinuation in 5 patients and dosage adjustment in 2 patients.
Sharkey et al.[36] (1996) Amphotericin B lipid complex (ABLC) 1.2 mg/kg/day for 2 weeks, followed by 2.5 mg/kg/day 3 times weekly for 4 weeks vs amphotericin B lipid complex (ABLC) 2.5 mg/kg/day for 2 weeks, followed	MC, OL, RCT Patients with AIDS presenting with their first episode of cryptococcal meningitis	N=55 12 weeks posttreatment follow-up	Primary: Clinical response, mycological response, overall response	Primary: No significant differences were observed in clinical, mycological, and overall responses between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
by 5.0 mg/kg/day 3 times weekly for 4 weeks vs amphotericin B lipid complex (ABLC) 5.0 mg/kg/day for 2 weeks, followed by 5.0 mg/kg/day 3 times weekly for 4 weeks vs amphotericin B deoxycholate (AmB) 0.7 mg/kg/day for 2 weeks, followed by 1.2 mg/kg/day 3 times weekly for 4 weeks After primary treatment, patients were given oral fluconazole.				
Brouwer et al.[38] (2004) Amphotericin B 0.7 mg/kg/day plus fluconazole 400 mg daily	OL, RCT Adult patients with HIV and a first episode of cryptococcal meningitis	N=64 10 weeks	Primary: Rate of reduction of CSF cryptococcal colony-forming units (CFU)	Primary: Early fungicidal activity occurred faster for patients receiving amphotericin B plus flucytosine than amphotericin B alone (P=0.0006), amphotericin B plus fluconazole (P=0.03), or amphotericin B plus flucytosine plus fluconazole (P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amphotericin B 0.7 mg/kg/day plus fluconazole 400 mg daily plus flucytosine 100 mg/kg/day vs amphotericin B 0.7 mg/kg/day plus flucytosine 100 mg/kg/day vs amphotericin B 0.7 mg/kg/day After 2 weeks, all four arms were treated with fluconazole 400 mg daily for 8 weeks and 200 mg daily thereafter.				
Saag et al.[34] (1992) Amphotericin B 0.3 mg/kg/day or an equivalent dose every other day	MC, RCT Patients 18 years of age and older with HIV and a positive CSF culture for *Cryptococcus neoformans*	N=194 10 weeks	Primary: Rate of treatment success (sterilization of CSF cultures)	Primary: Treatment was successful in 40% of the amphotericin B patients and 34% of the fluconazole patients (P=0.40). Disease progression occurred more frequently in the fluconazole group while discontinuation of study drug occurred more frequently in the amphotericin B group though neither difference was statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluconazole 400 mg loading dose orally then 200 mg daily Patients in the amphotericin B group may also have been treated with flucytosine 150 mg/kg/day according to investigator discretion.				
Pappas et al.[59] (2009) Amphotericin B deoxycholate 0.7 mg/kg/day for 14 days, followed by fluconazole 400 mg/day for 56 days (AmB) vs amphotericin B deoxycholate 0.7 mg/kg/day plus fluconazole 400 mg/day for 14 days, followed by fluconazole 400 mg/day for 56 days	RCT, OL, MC Patients ≥13 years of age who were experiencing a first episode of HIV-associated cryptococcal meningitis	N=143 Median 57-70 days	Primary: Safety and tolerability Secondary: Mortality and efficacy	Primary: More than 30% of patients in each arm experienced severe toxicities related to AmB or fluconazole. These events included hypomagnesemia, hypokalemia, anemia, AmB infusion intolerance, decreased renal function, psychosis, and subdural hematoma. Most of the toxicities were related to AmB. Neither of the combination therapy arms experienced a higher incidence of toxicities than the standard therapy arm. Except for nausea, the percentage of patients who experienced site-reported adverse events in the combination therapy arm was comparable to or less than the percentage in the standard arm who experienced site-reported adverse events. A greater percentage of patients experienced nausea in the combination therapy group compared to the standard therapy group (P=0.19). A greater percentage of patients in the AmB plus Fluc 800 arm than in the standard arm reported possible, probable, or definite treatment-associated adverse events that were dose limiting (14.3% vs 8.9%) or serious (12.2% vs 6.7%). The most frequent dose-limiting adverse events were related to a decrease in renal function. On average, all treatment arms experienced a decrease from baseline creatinine clearance level for days 7, 14, and 42.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(AmB plus Fluc 400) vs amphotericin B deoxycholate 0.7 mg/kg/day plus fluconazole 800 mg/day for 14 days, followed by fluconazole 800 mg/day for 56 days (AmB plus Fluc 800)				Secondary: Higher mortality was observed in the standard therapy arm than in the combination therapy arms (22.2%, 17%, and 18.4% for the AmB arm, the AmB plus Fluc 400 arm, and the AmB plus Fluc 800 arm, respectively). At day 14, a greater percentage of patients in the modified intention-to-treat population had experienced success in the AmB plus Fluc 800 arm than in the AmB arm; however, a smaller percentage of patients experienced success in the AmB plus Fluc 400 arm than in the AmB arm.
Chotmongkol et al.[29] (1997) Amphotericin B 0.3 mg/kg/day plus flucytosine 150 mg/kg/day plus itraconazole 400 mg/day (study group) vs amphotericin B 0.3 mg/kg/day plus flucytosine 150 mg/kg/day (control group)	OL, RCT Patients with acquired immunodeficiency syndrome (AIDS) and a diagnosis of cryptococcal meningitis	N=100 6 weeks	Primary: Clinical treatment outcomes, mean length of time until normalization of body temperature, mean time until negative cerebrospinal fluid (CSF) culture	Primary: Successful treatment was significantly higher in the study group compared to the control group (100% and 90% respectively, P=0.03). Mean length of time until normal body temperature was shorter in the study group compared to the control group (5.9 days and 8.8 days respectively, P=0.02). The mean length of time until the first negative CSF culture was 13.9 days in the study group and 13.3 days in the control group (P=0.66). Relapse rates were higher in the study group.
Bennett et al.[30] (1979)	PRO, RCT Patients with either	N=78 10 weeks	Primary: Cure rates and mortality	Primary: Cure or improvement was observed in 66% of patients in the combination group and in 47% of patients in the amphotericin B group (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amphotericin B 0.3 mg/kg/day plus flucytosine 150 mg/kg/day orally divided every 6 hours for 6 weeks vs amphotericin B 0.4 mg/kg/day for 42 days followed by 0.8 mg/kg every other day for 28 days	positive CSF smear or culture or clinical features compatible with cryptococcal meningitis plus a positive culture from another site or positive cryptococcal antigen test or evidence of intracranial cryptococcosis			There were 15 deaths in the amphotericin B group (47%) compared to 8 deaths in the combination group (24%, P<0.05).
Larsen et al.[32] (1990) Amphotericin B 0.7 mg/kg/day for 7 days then 3 times weekly for 9 weeks plus flucytosine 150 mg/kg/day orally in 4 doses for 10 weeks vs fluconazole 400 mg orally for 10 weeks	PRO, RCT Patients 18 years of age and older with evidence of cryptococcal meningitis, with or without AIDS	N=26 62 weeks	Primary: Clinical outcomes	Primary: After 10 weeks of treatment, 8 of 14 patients receiving fluconazole were considered failures while 0 of 6 patients taking amphotericin B plus flucytosine were considered failures (P=0.04). Conversion from positive to negative blood and CSF cultures was significantly slower in patients taking fluconazole compared to amphotericin B and flucytosine for CSF cultures (P=0.02). No significant difference was seen in the time to achieve mycological success for blood cultures (P=0.19).
de Gans et al.[31] (1992) Amphotericin B	OL, PRO, RCT Patients with suspected	N=28 6 weeks	Primary: Response to therapy, survival, relapse rates	Primary: Five of 14 patients in the itraconazole group showed a complete response and 7 showed a partial response.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.3 mg/kg/day plus flucytosine 150 mg/kg orally daily in 4 divided doses for 6 weeks vs itraconazole 200 mg twice daily for 6 weeks All patients completing the study then received itraconazole 200 mg daily as maintenance therapy.	cryptococcal meningitis			Twelve of 14 patients in the itraconazole group survived for more than 6 weeks. Ten of 11 patients in the amphotericin B and flucytosine group had a complete response. Ten of 11 patients in the amphotericin B and flucytosine group survived for more than 6 weeks. The difference in complete response between groups was significant and favored the amphotericin B plus flucytosine group (P=0.009). Overall, no significant difference in relapse rates was observed between original groups during the maintenance period (P=0.22). No significant difference in mean survival was observed between original treatment groups (P=0.65).
van der Horst et al.[37] (1997) Step 1 Amphotericin B 0.7 mg/kg/day plus flucytosine 100 mg/kg/day in 4 doses for 2 weeks vs amphotericin B 0.7 mg/kg/day for 2 weeks Step 2	DB, MC, RCT Patients were ≥13 years of age with a first episode of AIDS-associated cryptococcal meningitis	Step 1 N=381 Step 2 N=306 10 weeks	Primary: Mycological response at 2 and 10 weeks, clinical outcome at 2 and 10 weeks	Primary: Mycological response rates at the end of step 1 in patients receiving amphotericin B plus flucytosine or amphotericin B alone were 60% and 51%, respectively (P=0.06). Clinical response rates at the end of step 1 in patients receiving amphotericin B plus flucytosine or amphotericin B alone were 78% and 83%, respectively (P=0.18). There was no significant difference between the treatments in combined mycological and clinical response (P=0.12). Mycological response rates at the end of step 2 in patients receiving fluconazole and itraconazole were 72% and 60%, respectively. Clinical response rates at the end of step 2 in patients receiving fluconazole and itraconazole were 68% and 70%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluconazole 800 mg daily for 2 days, then 400 mg daily for 8 weeks vs itraconazole 600 mg daily for 3 days, then 200 mg 2 times daily for 8 weeks				There was no significant difference between fluconazole and itraconazole in mycological or clinical response.
Bicanic et al.[69] (2008) Amphotericin B deoxycholate 0.7 mg/kg/day plus flucytosine 25 mg/kg 4 times per day for 2 weeks (group 1) vs amphotericin B 1 mg/kg per day plus flucytosine 25 mg/kg 4 times per day for 2 weeks (group 2) After 2 weeks, patients received fluconazole 400 mg/day for 8 weeks and	RCT HIV-infected adults hospitalized with a first episode of cryptococcal meningitis	N=64 10 weeks	Primary: Mean rate of decrease in the number of *Cryptococcus* colony-forming units in the cerebrospinal fluid (CSF) or early fungicidal activity (EFA) Secondary: Rates of renal impairment and anemia, mortality at 2 and 10 weeks, and long-term survival during antiretroviral therapy	Primary: The rate of clearance of infection during the first 2 weeks of therapy was more rapid for group 2 than for group 1. The mean EFA was -0.56 log cfu/mL of CSF per day for group 2 and -0.45 log cfu/mL of CSF per day for group 1. Secondary: The mortality rate was 6% at 2 weeks and 24% at 10 weeks, with no difference between groups. Sixty-eight percent and 60% of patients were alive at 6 months and 1 year, respectively, of follow-up. There was no difference in survival rates between the 2 groups at any time point. There were no significant differences between groups 1 and 2 in measurements of renal impairment. A decrease in the hemoglobin level 12 g/dL developed in 50% and 71% of patients in groups 1 and 2, respectively (P=0.2). The percentage decrease in the hemoglobin level was greater for group 2 (95% CI, 2%–15%; P=0.01) and greater for women (95% CI, 4%–17%; P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
200 mg/day thereafter.				
Sloan et al.[68] (2008) Amphotericin B, flucytosine, and fluconazole given alone or in combination	MA HIV-infected adults with a first episode of cryptococcal meningitis	N=595 (5 trials) ≥2 weeks	Primary: Mortality, adverse events, proportion of patients with sterile cerebrospinal fluid (CSF) after 2 weeks of therapy	Primary: <u>Fluconazole and flucytosine vs fluconazole</u> There was no difference in death rate at 14 days (RR 0.4; 95% CI, 0.14 to 1.11) or at six months (RR 0.77; 95% CI, 0.57 to 1.05). There were no major adverse events in either group. There was no difference in number of patients with sterile CSF at 2 months after treatment (RR 0.4; 95% CI, 0.11 - 1.36). <u>Amphotericin B vs amphotericin B and flucytosine</u> There was no difference in the proportion deaths at 14 days (RR 1.1; 95% CI, 0.51 to 2.4). There was no difference in major adverse events between the two treatment arms (RR 0.94; 95% CI, 0.29 to 3.03).There was higher proportion of patients with sterile CSF cultures at 14 days in the group of patients receiving flucytosine (RR 0.81; 95% CI, 0.68 to 0.98). <u>Amphotericin B vs amphotericin B, flucytosine and fluconazole</u> There was no difference in the proportion deaths at 14 days or 10 weeks (RR 2.0; 95% CI, 0.2 to 19.91 and RR 1.0; 95% CI, 0.24 to 4.23, respectively). There were no serious adverse events in either group. There was no difference in the proportion of patients with sterile CSF at 14 days (RR 0.5; 95% CI, 0.11 to 2.35). <u>Amphotericin B and flucytosine vs amphotericin B, flucytosine and fluconazole</u> There was no difference in the proportion deaths at 14 days or 10 weeks (RR 1.07; 95% CI, 0.07 to 15.57 and RR 1.07; 95% CI, 0.07 to 15.57, respectively). There were no serious adverse events in either group. There was no difference in the proportion of patients with sterile CSF at 14 days (RR 1.6; 95% CI, 0.56 to 4.58). <u>Amphotericin B and flucytosine vs amphotericin B and fluconazole</u> There was no difference in the proportion of deaths at 14 days or 10 weeks (RR 0.21; 95% CI, 0.03 to 1.62 and RR 0.15; 95% CI, 0.02 to 1.1). There were no serious adverse events in either group. There was no difference in the amount of patients with sterile CSF at 14 days (RR 2.13 95% CI 0.65

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				to 7.04). <u>Amphotericin B vs amphotericin B and fluconazole</u> There was no difference in the proportion deaths at 14 days or 10 weeks (RR 0.4; 95% CI, 0.09 to 1.77 and RR 0.43; 95% CI, 0.13 to 1.37). There were no serious adverse events in either group. There was no difference in the amount of patients with sterile CSF at 14 days (RR 0.67; 95% CI, 0.13 to 3.47). <u>Amphotericin B and fluconazole vs amphotericin B, flucytosine and fluconazole</u> There was no difference in the proportion deaths at 14 days or 10 weeks (RR 5.0; 95% CI, 0.66 to 38.15 and RR 2.33; 95% CI, 0.73 to 7.45). There were no serious adverse events in either group. There was no difference in the amount of patients with sterile CSF at 14 days (RR 0.75; 95% CI, 0.2 to 2.83). <u>Standard dose amphotericin B and flucytosine vs high dose amphotericin B and flucytosine</u> There was no difference in the proportion of deaths at 14 days or 10 weeks (RR 0.34; 95% CI, 0.04 - 3.44 and RR 0.76; 95% CI 0.03 - 1.83, respectively). There was no difference in major adverse events defined as side effects of treatment leading to the study interventions being terminated (RR 0.23; 95% CI, 0.03 - 1.83). The proportion of patients with sterile CSF at 14 days was not different between the two treatment groups (RR 1.13; 95% CI, 0.43 - 2.94). <u>Amphotericin B vs liposomal amphotericin B</u> There was no difference in the proportion of patients who had a clinical response after 3 weeks of treatment in the liposomal amphotericin B group and the amphotericin B group (RR 0.95; 95% CI, 0.67 - 1.33). There was no difference in the proportion of deaths at 14 days, 10 weeks or 6 months. At 6 months, 2/15 patients who received liposomal amphotericin B had died and 1/13 patients who received amphotericin B had died (RR 1.73; 95% CI, 0.12 - 59.4). Major adverse events were less common in patients who received liposomal amphotericin B (RR 0.19; 95% CI, 0.05 - 0.74). There was no difference in the patients with sterile CSF at 14 days in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				either group (RR 6.0; 95% CI, 0.91 to 39.41).
Empirical Therapy				
Martino et al.[42] (2005) Amphotericin B lipid complex (ABLC) 3 mg/kg/day for minimum of 7 days and a maximum of 12 weeks	OL, PRO Patients with hematological malignancy and a documented or suspected invasive mycosis	N=74 Up to 12 weeks	Primary: Clinical response (overall response= complete and partial response; complete= resolution of signs and symptoms of infection and resolution of microbiological abnormalities; partial= substantial improvement)	Primary: The overall response rate was 67% after a median of 18 days of therapy. The complete and partial response rates were 56% and 11%, respectively Patients with invasive aspergillosis (IA) had an overall response rate of 61% and patients with non-cultured invasive mold infections (IMI) had an overall response rate of 67%. The overall response rate of patients who entered the study during neutropenia was 90%.
Subria et al.[56] (2004) Amphotericin B lipid complex (ABLC) 1 mg/kg/day vs amphotericin B deoxycholate 0.6 mg/kg/day Therapy was continued until defervescence and recovery of neutrophil count to >0.5 × 10^9/L.	PRO, RCT Patients ≥18 years of age hospitalized with neutropenic fever due to chemotherapy for a hematological malignancy or after undergoing autologous hematopoietic stem cell transplantation (HSCT)	N=105 End of therapy	Primary: Toxicity and response to therapy	Primary: The incidence of nephrotoxicity was significantly lower in the ABLC group compared to the amphotericin B group (P=0.003). A significantly higher proportion of patients in the amphotericin B group experienced increases in serum creatinine compared to the ABLC group (P=0.009). The mean absolute increase in serum creatinine from baseline was significantly lower in the ABLC group compared to the amphotericin B group (P=0.01). Hypokalemia was significantly more frequent in the amphotericin B group compared to the ABLC group (P=0.01). There were no statistically significant differences in infusion-related adverse events between groups (P>0.2). Significantly more patients in the ABLC group had a satisfactory response to therapy compared to those in the amphotericin group (P=0.018).
Wingard et al.[40]	DB, MC, RCT	N=244	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2000) Amphotericin B lipid complex (ABLC) 5 mg/kg/day vs amphotericin B liposome (L-AMB) 3 or 5 mg/kg/day Treatment was continued for up to 3 days after neutrophil recovery to a maximum of 42 days.	Patients 2 years of age and older with neutropenia and a suspected fungal infection	7 day posttreatment follow-up	Frequency of infusion-related chills/rigors during infusion and for up to 1 hour after infusion on day 1; clinical efficacy	There was a lower frequency of chills/rigors on day 1 in the L-AMB group compared to the ABLC group (P<0.001). There was significantly less nephrotoxicity associated with L-AMB compared to ABLC (P<0.01). There was no significant difference observed in successful response between the groups. A lower portion of patients in the L-AMB group discontinued therapy due to an adverse event compared to the ABLC group (P<0.001).
Fleming et al.[41] (2001) Amphotericin B lipid complex (ABLC) 3-5 mg/kg/day vs amphotericin B liposome (L-AMB) 3-5 mg/kg/day	RCT Patients with leukemia who developed suspected or documented fungal infections	N=75 End of treatment (mean 10-15 days)	Primary: Antifungal response Secondary: Safety	Primary: The overall response in patients treated for suspected or proven fungal infections was 70% in the ABLC group and 50% in the L-AMB group (P=0.15). Complete or partial response was observed in 63% of patients in the ABLC group and 39% of patients in the L-AMB group in the intent-to-treat population (P=0.03). Among patients receiving empiric therapy, resolution of fever and total or partial clearing of pulmonary infiltrates was observed in 94% of patients in the ABLC group and in 62% of patients in the L-AMB group (P=0.02). Secondary: Significantly more patients in the ABLC group experienced mild-to-moderate infusion-related adverse events compared to those in the L-AMB

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group (P=0.002). Significantly more patients in the L-AMB group experienced mild elevations in hepatic enzymes compared to the ABLC group (P=0.02). There were no significant differences between groups in any other safety parameter (P>0.05).
Cordonnier et al.[61] (2008) Amphotericin B liposome 10 mg/kg once per week as prophylaxis Treatment was received for 4 consecutive weeks for AL patients and 8 consecutive weeks for SCT patients.	OL, MC Patients ≥18 years old who underwent a standard myeloablative conditioning regimen and acute graft vs host disease cyclosporin prophylaxis for stem cell transplantation (SCT) or underwent first or second induction therapy after relapse or consolidation therapy for acute leukemia (AL) and had expected neutropenia $<0.5\times10^9$ neutrophils/L for at least 2 weeks	N=29 8 weeks	Primary: Rate of adverse events	Primary: During the prophylaxis period, all patients reported at least one AE. The most frequent adverse events (AEs) related to study drug were infusion-related reactions, 12 of which (from a total of 76 infusions) led to increased infusion duration for better tolerance. Because the rate of common toxicity criteria (CTC) grade 3–4 adverse events was above the10% limit assigned by the protocol, it was decided by the independent data review committee to stop the inclusion of SCT subjects. In the AL group, 16 serious AEs were reported for ten patients and 8 serious AEs were reported for four SCT patients. Two serious AEs (anuria and anaphylactic shock), both in the SCT group, were considered to be related to the prophylactic antifungal treatment. Two episodes of hypokalemia were reported and were thought to be related to the study drug in the AL group. Renal and electrolyte disorders were frequent; however, they were frequently unrelated to the prophylactic treatment. All SCT patients received cyclosporin A. Analysis of serum creatinine values up to 1 month after the last infusion demonstrated an increase ≥2-fold the baseline value in 2/21 AL patients and 2/8 SCT patients. Discontinuation of prophylactic treatment occurred in three AL patients (14%) due to four AEs (fever, bronchopulmonary aspergillosis, *Escherichia coli* sepsis and positive *Candida* serology); none of these AEs were related to study treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Discontinuation of prophylactic treatment occurred in eight SCT patients (100%) due to 11 adverse events: 3 were not related to study treatment (renal insufficiency, thrombotic microangiopathy and bronchopulmonary aspergillosis) and 8 were reported to be related to study treatment (dyspnea, chest pain, abdominal pain, nausea, tubulointerstitial nephritis, renal insufficiency, anuria and anaphylactic shock). No AE related to the study drug led to discontinuation of prophylactic treatment in AL patients. In SCT patients, eight AEs (in six patients) reported to be related to study treatment led to treatment discontinuation. Enrolment was discontinued in the SCT group as recommended by the independent data review committee in accordance with the 10% limit of AEs (CTC grade 3–4) fixed by the protocol. Thirteen AL patients and four SCT patients received antifungal empirical treatment during the prophylaxis period. The median time to first empirical antifungal treatment was 17 days in AL patients and 7.5 days for SCT patients.
Ellis et al.[39] (2006) Amphotericin B liposome 3 to 5 mg/kg/day for at least 10-14 days vs caspofungin 70 mg loading dose then 50 mg daily for at least 10-14 days Treating physician could escalate	RETRO Patients with acute hematological malignancies with prolonged neutropenia or invasive fungal infections	N=73 7 day posttreatment follow-up	Primary: All-cause mortality within 7 days of completion of antifungal therapy, response to treatment, toxicity Secondary: All antifungal drug administration during each hospital admission	Primary: Significantly more deaths were seen in patients following caspofungin therapy compared to liposomal amphotericin B therapy (P=0.013). Overall, response to therapy did not differ significantly between treatment groups (P>0.16). Significantly more patients experienced treatment failure due to a breakthrough invasive fungal infection in the caspofungin group compared to the amphotericin B group (P=0.047). The proportion of events treated with amphotericin B which had at least 1 adverse event was significantly higher compared to the caspofungin group (P=0.02). Significantly more patients in the amphotericin B group experienced episodes of hypokalemia (P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amphotericin B dose to 10 mg/kg.				A similar proportion of drug discontinuations was observed due to adverse effects between the groups (P=0.48). Secondary: There were a total of 97 episodes of treatment with either caspofungin or liposomal amphotericin B and results were similar to those seen in the primary efficacy endpoints.
Maertens et al.[80] (2010) Amphotericin B liposome (L-AMB) 3 mg/kg daily vs caspofungin 70 mg/m^2 loading dose on day 1, then 50 mg/m^2 daily	MC, DB, RCT Patients 2 to 17 years of age who had received chemotherapy for cancer or had undergone HSCT, had received parenteral broad-spectrum antibacterial therapy for ≥96 hours, and were neutropenic and febrile	N=83 Up to 28 days	Primary: Safety and tolerability Secondary: Efficacy	Primary: Serious clinical adverse events that were considered to be drug related were reported in 1 (1.8%) caspofungin recipient (hypotension) and 3 (11.5%) L-AMB recipients (hyperbilirubinemia; circumoral edema; and angioneurotic edema with dyspnea, laryngospasm, and tachycardia); all 4 patients discontinued the intended course of therapy. Three patients died during the study: 2 (3.6%) in the caspofungin group and I (3.8%) in the L-AMB group. Secondary: A favorable overall response was observed in 46.4% of patients who received caspofungin and 32.0% of those who received L-AMB; however, the 95% CIs for the treatment groups overlapped.
Johansen et al.[43] (2002) Amphotericin B vs fluconazole	MA Patients with cancer complicated by neutropenia	N=3,798 (17 trials) Various durations	Primary: Mortality, invasive fungal infections, colonization, use of additional antifungal therapy, adverse effects leading to discontinuation	Primary: No significant difference was observed between fluconazole and amphotericin B on mortality (P>0.1). No significant difference was observed between fluconazole and amphotericin B on the rate of invasive fungal infection (P>0.4). No significant difference was observed between fluconazole and amphotericin B on fungal colonization (P>0.3). No significant difference was observed overall between groups in the use of additional antifungal therapy (P>0.1). Significantly more patients receiving amphotericin B dropped out of the study due to adverse effects (P<0.009).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
van't Wout et al.[44] (1991) Amphotericin B 0.6 mg/kg/day IV vs itraconazole 200 mg orally 2 times daily Some patients treated with amphotericin B also received flucytosine at 150 mg/kg/day. In these cases, the amphotericin B dose was 0.3 mg/kg/day.	MC, RCT Neutropenic patients with proven or highly suspected fungal infections	N=40 End of therapy	Primary: Response to therapy (at least 50% decrease in size of initial site or severity of infection or resolution of all signs of infection)	Primary: Response to treatment was observed in 63% of itraconazole patients and 56% of amphotericin B patients (P>0.90).
Schuler et al.[62] (2007) Amphotericin B (AMB) IV 0.7-1.5 mg/kg/day vs itraconazole 200 mg IV every 12 hours for 2 days, followed by 200 mg once daily	RCT, OL Hospitalized adult patients with hematological malignancy treated with myelosuppressive therapy and/or who were allogeneic/ autologous bone marrow or blood stem cell transplant recipients	N=162 28 days	Primary: Permanent discontinuation of study medication due to any adverse event Secondary: Response and success rate for both treatment groups	Primary: Significantly fewer itraconazole patients discontinued treatment due to any adverse event (22.2 vs 56.8% AMB; P<0.0001). The main reason for discontinuation was a rise in serum creatinine (1.2% itraconazole vs 23.5% AMB). Renal toxicity was significantly higher and more drug-related adverse events occurred in the AMB group. Secondary: Intention-to-treat (ITT) analysis showed favorable efficacy for itraconazole; response and success rate were both significantly higher than for AMB (61.7 vs 42% and 70.4 vs 49.3%, both P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Treatment failure was reduced in itraconazole patients (25.9 vs 43.2%), primarily due to better tolerability.
Mandhaniya et al.[77] (2011) Amphotericin B 0.5 mg/kg/day 3 times per week vs voriconazole 6 mg/kg/dose for 2 doses, then 4 mg/kg/dose BID	RCT, OL, SC Pediatric patients <15 years of age with ALL or AML undergoing induction chemotherapy	N=100 Variable duration	Primary: Failure of prophylaxis indicated by proven/probable/ possible or suspected fungal infection or treatment discontinuation owing to side effects, adverse events	Primary: In the voriconazole arm, 28% of patients failed antifungal prophylaxis compared to 34% of patients in the amphotericin arm (P=0.66). There was no significant difference in the proven, possible, or probable fungal infections in the two study arms. Drug related serious adverse events were 6% and 30% in voriconazole and amphotericin B treated patients, respectively (P<0.01). All patients on amphotericin B experienced infusion-related toxicity such as fever, chills, and/or rigors and almost half of them had hypokalemia. Abdominal pain, hyperbilirubinemia, and macular skin rashes were observed more in the voriconazole arm.
Gotzsche et al.[45] (2002) Amphotericin B, fluconazole, ketoconazole, itraconazole, miconazole, placebo	MA Patients with cancer and neutropenia from chemotherapy or bone marrow transplants	N=4,155 (31 trials) Various study durations	Primary: Mortality Secondary: Invasive fungal infections, colonization, use of additional antifungal therapy	Primary: No significant differences were observed between the groups on mortality (P>0.08). Secondary: Invasive fungal infections decreased significantly with amphotericin B, fluconazole, and itraconazole (P<0.04) but not with miconazole or ketoconazole (P>0.2). Definitions of fungal colonization differed greatly between studies, though the effect of prophylaxis on colonization was significant for amphotericin B, fluconazole, itraconazole, and ketoconazole (P<0.02) but not for miconazole (P=0.8) Significantly more patients who received placebo or no treatment required additional antifungal therapy.
Clarkson et al.[57] (2007) Medications not absorbed from GI (amphotericin B,	MA Patients with cancer receiving chemotherapy, radiation, or both	N=4,226 (28 trials) Variable duration	Primary: Prevention of oral candidiasis Secondary: (If available) relief	Primary: Drugs absorbed or partially absorbed from the GI tract were found to significantly decrease the incidence of oral candidiasis compared to non-absorbed drugs (P<0.016). Drugs absorbed or partially absorbed from the GI tract were found to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin) vs medications absorbed from the GI tract (fluconazole, ketoconazole, itraconazole) vs medications partially absorbed from the GI tract (miconazole, clotrimazole) vs placebo			of pain, amount of analgesia, relief of dysphagia, incidence of systemic infection, duration of hospital stay, cost of oral care, patient quality of life, death, use of empirical antifungal therapy, toxicity, compliance	significantly decrease the incidence of oral candidiasis compared to placebo or no treatment (P<0.004). Secondary: Significantly fewer patients who were treated with drugs absorbed from the GI tract required empiric antifungal therapy compared to placebo or no treatment (P=0.04). This effect was not seen in patients treated with drugs which are partially absorbed (P=0.4). This outcome was not analyzed in any study on non-absorbable drugs. No significant differences were observed between groups in any other secondary endpoint.
Violaris et al.[78] (2010) Nystatin 100,000 units divided in each side of the mouth every 6 hours vs fluconazole 4	RCT, OL Very low birth-weight neonates (<1.5 kg at birth)	N=80 Variable duration	Primary: Rate of systemic fungal infection Secondary: Mortality	Primary: Systemic fungal infection developed in two infants (5.3%) in the fluconazole group and six infants (14.3%) in the nystatin group (RR, 0.37; 95% CI, 0.08 to 1.72). Secondary: There were no deaths in the fluconazole group and six deaths in the nystatin group (P=0.03). Two infants died of neonatal sepsis, and four deaths were related to necrotizing enterocolitis and/or spontaneous intestinal perforation. No deaths were due to systemic fungal infection.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/day				
Aydemir et al.[79] (2011) Nystatin 100,000 units every 8 hours by orogastric tube vs fluconazole 3 mg/kg IV every third day vs placebo	RCT, DB Very low birth-weight neonates (<1.5 kg at birth)	N=278 4-6 weeks	Primary: Prevention of fungal colonization and infection Secondary: Mortality, incidence of bacterial sepsis, necrotizing enterocolitis, threshold retinopathy of prematurity requiring surgery, severe intraventricular hemorrhage, and bronchopulmonary dysplasia	Primary: Fungal colonization occurred less frequently in the fluconazole (10.8%) and nystatin (11.7%) groups than in the placebo group (42.9%; P<0.001). Invasive fungal infection was less frequent in the fluconazole (3.2%) and nystatin groups (4.3%), as compared with in the placebo group (16.5%; P<0.001). Secondary: The overall mortality was similar among the three groups (8.6% in the fluconazole group and 8.5% in the nystatin group, as compared with 12.1% in the placebo group; P=0.64). There were no significant differences in other secondary outcomes. No serious adverse effects of the fluconazole or nystatin therapy were documented.
Histoplasmosis				
Johnson et al.[48] (2002) Amphotericin B liposome 3 mg/kg/day for 2 weeks (induction therapy) vs amphotericin B deoxycholate 0.7 mg/kg/day for 2 weeks (induction	DB, MC, RCT Patients with AIDS and disseminated histoplasmosis infection	N=81 12 weeks	Primary: Clinical success Secondary: Time to defervescence, mycological efficacy, change in *H capsulatum* antigen levels in the urine and serum at week 2, rates of infusion toxicity and nephrotoxicity	Primary: Clinical success following induction therapy was observed in 88% of liposomal amphotericin B patients compared to 64% of amphotericin B patients (P=0.014). Consolidation therapy was successful in 88% of patients in the liposomal amphotericin B group and in 93% of patients in the amphotericin B group (P>0.2). There was no significant difference in negative cultures between groups at the end of consolidation therapy. Clinical and mycological outcomes could not be assessed at week 12 due to limited data.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy) All patients in whom induction therapy was successful received itraconazole for 10 additional weeks.				Secondary: The median time to defervescence was 3 days for both therapies. There was no significant difference between groups in time to negative culture (P>0.2). *H capsulatum* clearance was similar between groups. Significantly more patients treated with amphotericin B experienced infusion related toxicity compared to those in the liposomal amphotericin B group (P=0.002). Nephrotoxicity occurred in significantly more patients in the amphotericin B group compared to the liposomal amphotericin B group (P=0.003). Toxicities led to discontinuation of therapy in a similar number of patients in both groups (P=0.19).
Wheat et al.[47] (2001) Amphotericin B liposome 3 mg/kg/day for 2 weeks, followed by itraconazole 200 mg 2 times daily for 10 weeks vs itraconazole 300 mg orally 2 times daily for 3 days then 200 mg 2 times daily for 12 weeks	OL, CS Patients 13 years of age and older with HIV infection and first episode of disseminated histoplasmosis	N=110 12 weeks	Primary: Mycological response (negative blood cultures), time to negative blood cultures	Primary: By the end of the second week of therapy, blood cultures were negative in over 85% of amphotericin B patients compared to 53% of itraconazole patients (P=0.0008). By 12 weeks of therapy, cultures were negative in all patients in both groups. After 2 weeks of therapy, serum antigen levels fell by a significantly greater amount in the amphotericin B group compared to the itraconazole group (P=0.02). After 2 weeks of treatment, serum antigen levels were negative in 28% of the amphotericin B group and 20% of the itraconazole group (P=0.55). After 2 weeks of therapy, urine antigen levels were below the detection limit in 19% of amphotericin B patients and 3% of itraconazole patients (P=0.06). After 2 weeks of therapy, urine antigen levels fell by a significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				greater amount in the amphotericin B group compared to the itraconazole group (P<0.0005). By 12 weeks of therapy, there was no significant difference in the proportion of patients with undetectable serum and urine antigen levels in either group (P<0.80).
Leishmaniasis				
Sundar et al.[51] (2004) Amphotericin B deoxycholate 1 mg/kg/day every other day for 15 infusions (Group A) vs amphotericin B liposome 2 mg/kg/day for 5 infusions (Group B) vs amphotericin B lipid complex 2 mg/kg/day for 5 infusions (Group C)	OL, RCT Patients with signs and symptoms of visceral leishmaniasis (VL) confirmed microscopically	N=153 6 month posttreatment follow-up	Primary: Apparent cure (day 19), definite cure (posttreatment follow-up)	Primary: On day 19, no significant differences in apparent cure were observed between the treatment groups. During the follow-up period, overall definite cure rates did not differ between groups (P>0.05). On day 7, significantly fewer patients in Groups B and C had fever compared to Group A (P<0.05); however, only 4 infusions of amphotericin B deoxycholate had been given compared to all doses of the lipid formulations. Overall duration of fever was shorter in Group B compared to Group C (P<0.05) and both were shorter than Group A (P<0.05).
Sundar et al.[50] (2002) Amphotericin B liposome	DB, MC, RCT Patients of any age with visceral leishmaniasis	N=84 6 month posttreatment follow-up	Primary: Apparent cure (resolution of fever, regression of splenomegaly,	Primary: There were no significant differences between groups in apparent or definite cure.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.75 mg/kg/day for 5 days vs amphotericin B liposome 1.5 mg/kg/day for 5 days vs amphotericin B liposome 3 mg/kg/day for 5 days			absence of parasites in splenic or marrow smear at the end of 2 weeks of therapy), definite cure (absence of signs and symptoms of VL after 6 months of follow-up	
Miscellaneous				
Anaissie et al.[46] (1998) Amphotericin B colloidal dispersion (ABCD) 4-6 mg/kg/day for 2 weeks after resolution of signs and symptoms of infection (up to 6 weeks)	MC, OL Patients with invasive fungal infections (including *Aspergillus*, *Candida*, *Histoplasma*, cryptococcosis, and *Coccidioides*) and impaired renal function	N=133 3 month posttreatment follow-up	Primary: Clinical and mycological response (complete=no clinical or mycological evidence of active infection; partial= improvement in signs and symptoms but not complete response)	Primary: At the end of treatment, 67.2% of patients had a complete or partial response, and 32.8% were considered treatment failures (continued fungal infections, additional treatment required). The highest cure rates were seen in patients with candidiasis (56.6%, complete response). Of patients who had previously received amphotericin B therapy, 64% had a complete or partial response at the end of therapy, while 77% of patients who had not previously received amphotericin B therapy had a complete or partial response. At the end of the follow-up period, 34.5% of patients had a complete or partial response to therapy. No overall trend for increased creatinine levels was observed.
Walsh et al.[49] (1999)	MC, OL Pediatric patients	N=111 4 week	Primary: Clinical response (complete=resoluti	Primary: No significant differences were seen in renal function, serum creatinine, serum potassium, or serum magnesium compared to baseline values

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amphotericin B lipid complex (ABLC) 5 mg/kg/day	<18 years of age with an invasive fungal infection and one or more of the following: progression of infection despite antifungal treatment, onset of renal dysfunction secondary to amphotericin B or other nephrotoxic agents, intolerable infusion-related toxicity, or pre-established renal dysfunction	posttreatment follow-up	on of signs and symptoms of invasive mycosis; partial=substantial reduction in signs and symptoms), safety	(P>0.054). The overall response rate (complete and partial responses) was 64% for filamentous fungi infections (including Zygomycetes and *Fusarium* species), and 56% for aspergillosis. The overall response rate for candidiasis was 81% and was similar for disseminated disease (82%), single organ disease (75%), and candidemia (83%) and no significant difference was observed between types of *Candida* infection.
Cordonnier et al.[65] (2007) <u>Study 1</u> Amphotericin B liposome (L-AMB) 5 mg/kg/day vs amphotericin B deoxycholate <u>Study 2</u> Amphotericin B liposome (L-AMB) 1 mg/kg/day	RETRO Patients with documented or suspected neutropenia-associated invasive fungal infections, or invasive aspergillosis	N=69 Variable duration	Primary: Favorable response (complete or partial response) and survival	Primary: A favorable response with L-AMB was observed in 51% of cases: 55% of cases with proven invasive filamentous fungal infections (IFFI) and 49% of cases with probable IFFI. Treatment with L-AMB as the first-line therapy showed a higher favorable response (61%) compared with the administration of the second-line therapy (32%). Patients with severe neutropenia at baseline showed a response similar to that of patients without severe neutropenia, with 47% of patients and 54% of patients achieving a favorable response, respectively. In patients with hematological disease, a favorable response was observed in 51% of patients. Of these, 44% who received allogeneic stem cell transplantation (SCT) and 57% who received autologous SCT showed a favorable response with L-AMB. Favorable response rates varied by the site of infection, ranging from 44% for pulmonary infections, 64% for sinus/nasal infections, 57% for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs Amphotericin B liposome (L-AMB) 4 mg/kg/day Study 3 Amphotericin B liposome (L-AMB) 7.5 - 15 mg/kg/day				disseminated infections and one of one case each for subcutaneous abscess, pericarditis, and mastoiditis. Of the patients with probable or proven IFFI, 51% treated with L-AMB survived to the last follow-up visit. Of these surviving patients, 23 of 35 patients had survival documented to ≥12 weeks after the initiation of treatment. For the remaining 12 patients whose last study visit was <12 weeks following the initiation of L-AMB treatment,
Paterson et al.[60] (2008) Amphotericin B colloidal dispersion (ABCD)	OBS Adult or pediatric patients who received at least one dose of amphotericin B colloidal dispersion	N=170 12 weeks	Primary: Rate of pre-medication use and the incidence of infusion-related reactions (IRRs) Secondary: Response rates, mortality rates, adverse event rates and rates of nephrotoxicity/ hepatotoxicity	Primary: Pre-medications were used in 89.8% of all infusions. Overall, 10.2% of the infusions had no pre-medication, 36.7% had one pre-medication, 38.7% had two pre-medications, 14.2% had three pre-medications and two infusions had four pre-medications. Corticosteroids were the most common class of drugs used for pre-medication (67% of the infusions); antihistamines were used in 41.4% of the infusions; paracetamol and metamizole were used in 24.3% and 20.7% of the ABCD infusions, respectively. Overall, IRRs occurred in 12% of the ABCD infusions. The rate of IRRs following the first infusion only was 32.9%. The most common IRR was fever (7.0%), followed by chills (6.9%) and rigors (5.3%); other IRRs occurred in 1.2% of the infusions or less. Pre-medication was associated with an overall 51.9% decreased incidence of IRRs; not receiving pre-medication was associated with a significant increased risk of an IRR (OR: 2.4, 95% CI 1.51–3.80, P=0.0001). The IRR rate in pre-medicated ABCD infusions was 10.8% while the IRR rate associated with ABCD infusions that did not have pre-medication was 22.4%, P<0.001. Following the first infusion only, the IRR rate in premedicated ABCD infusions was 31.5% while the IRR rate associated with ABCD infusions that did not have premedication was 42.9% (P=0.30). The incidence of IRRs following pre-medicated infusions decreased by

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				50% from day 1 to day 2 (31.5% to 15.6%) of ABCD therapy and by 58% from day 2 to day 3 (15.6% to 6.5%) of therapy. After the third day of ABCD therapy, the IRR rate remained relatively constant and did not exceed 9.1%. The incidence of IRRs following infusions that were not pre-medicated decreased from day 1 to day 2 (from 42.9% to 26.7%; 38% decrease) and from day 2 to day 3 (26.7% to 20.0%, 25% decrease); however, from day 3 to day 10 the rate of IRRs was erratic and generally well above the rate of the premedicated infusions. There was a significantly lower incidence of IRRs following infusions where pre-medication with corticosteroids was given (8.1%) compared with infusions where corticosteroids were not given (19.9%), P<0.001. In particular, dexamethasone appeared to have strong effect; following the first infusion of ABCD, 12.0% of the infusions where dexamethasone was given had an IRR versus 36.6% of the infusions where dexamethasone was not given (P=0.016), and for overall infusions, 7.7% of the infusions where dexamethasone was given had an IRR versus 12.9% of the infusions where dexamethasone was not given (P=0.03). Pre-medication with an antihistamine or paracetamol was associated with an increased IRR rate. Secondary: Information on clinical outcome at 12 weeks after initiation of ABCD was available on 143 participants. Fifty-two percent of the participants positively responded to ABCD, 8% of the participants failed to respond to treatment and 39.2% of the participants had indeterminate information on status at 12 weeks post-treatment start. Twenty-five percent of the participants were deceased by 12 weeks after the onset of ABCD therapy. Nearly half of the deaths were due to the patient's underlying health condition (44%); 30% were due to an infection other than the fungal infection being primarily treated in the study, 12% were reported as being due to a combination of the patient's underlying health condition and the primary fungal infection, 9.3% deaths were reported as being due to the primary fungal infection alone, 7.0% deaths were reported as due to graft versus host disease, 7.0% due to multi-organ failure, 4.7% due to respiratory failure, 4.7% due to septic shock without

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				identification of the causal agent and one death each due to multidrug-resistant *Pseudomonas*, CMV pneumonitis and renal insufficiency. There was a trend towards lower mortality rates between participants who received pre-medication with a corticosteroid (21.9%) versus no pre-medication with a corticosteroid (35.7%), but this was not statistically significant (P=0.07). Fifteen percent of the participants had a treatment emergent adverse event; eight of these were serious adverse events.

Drug regimen abbreviations: IV=intravenously
Study abbreviations: AC=active control, CS=comparative study, DB=double blind, DD=double dummy, DR=dose ranging, MC=multi-center, OL=open label, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind
Miscellaneous abbreviations: AIDS=acquired immunodeficiency syndrome. CSF=cerebrospinal fluid, HIV=human immunodeficiency virus

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 the Polyenes

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amphotericin B	injection	N/A	N/A	$$$
Amphotericin B cholesteryl sulfate complex	injection	Amphotec®	$$$$$	N/A
Amphotericin B lipid complex	injection	Abelcet®	$$$$$	N/A
Amphotericin B liposome	injection	AmBisome®	$$$$$	N/A
Nystatin	powder for suspension, suspension, tablet	N/A	N/A	$-$$$

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

X. Conclusions

The polyenes are approved for the treatment of numerous fungal infections. Conventional amphotericin B (deoxycholate) has been available for several decades; however, its use is associated with a high incidence of infusion-related adverse events and nephrotoxicity. There are three lipid formulations of amphotericin B that are currently available, including amphotericin B colloidal dispersion, amphotericin B lipid complex and amphotericin B liposome. These agents were developed to minimize toxicity that is associated with conventional amphotericin B. Nystatin and conventional amphotericin B are both available in a generic formulation.

There are many guidelines that define the appropriate place in therapy for the polyenes.[7,9-17] Amphotericin B is recommended as specific therapy for the treatment of aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcal disease, histoplasmosis, sporotrichosis, as well as for prophylaxis in patients with chemotherapy-induced neutropenia.[7,9-17] The specific amphotericin B formulation that is recommended (conventional vs lipid) is dependent upon the location of the infection, pregnancy status, as well as the age of the patient (refer to Table 3 for further discussion). According to the prescribing information, the use of amphotericin B (all formulations) should be reserved for the treatment of patients with progressive and potentially life-threatening fungal infections. It should not be used to treat noninvasive forms of fungal disease, such as oral thrush, vaginal candidiasis, and esophageal candidiasis in patients with normal neutrophil counts.[1-5]

Several clinical trials have directly compared the efficacy and safety of the various amphotericin B formulations. Studies have demonstrated similar efficacy among the conventional and lipid formulations.[6,19,33,40-41,51,68] Rates of adverse events, including infusion-related reactions and nephrotoxicity, were higher with the conventional formulation than with the lipid formulations.[19-20,48,56,68] Amphotericin B lipid complex and amphotericin B liposome have also been shown to be comparable in efficacy.[40-41,51] Few studies have demonstrated greater clinical and/or mycological response rates with one amphotericin B formulation over another.[20,48,56] Studies have demonstrated similar efficacy when amphotericin B (all formulations) was compared to antifungal agents in other classes.[22-28,34,43-45,72-75,77,80]

Nystatin is approved for the treatment of gastrointestinal and oral cavity candidiasis.[1-3] Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches or nystatin suspension.[11] For moderate-to-severe infections or refractory disease, oral and intravenous therapy with other antifungal agents is recommended.[11] Studies have demonstrated greater clinical and microbiologic response rates with fluconazole compared to nystatin.[52-54,78]

There is insufficient evidence to support that one brand polyene is more efficacious than another. Since amphotericin B is not indicated as first-line therapy for the management of common infectious diseases that would be seen in general use, formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand polyenes 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 polyene 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Pyrimidines
AHFS Class 081432
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I. Overview

Flucytosine is approved for the treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus*.[1-3] It should be used in combination with amphotericin B because of the emergence of resistance. Flucytosine is converted to fluorouracil inside the fungal cell.[1-3] Fluorouracil exerts its antifungal activity through the subsequent conversion to several active metabolites. These metabolites inhibit protein synthesis by being falsely incorporated into fungal RNA, or interfere with the biosynthesis of fungal DNA through the inhibition of the enzyme thymidylate synthetase.

The pyrimidines that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The topical antifungals were previously reviewed with the skin and mucous membrane agents (AHFS 840408) and are not included in this review. Flucytosine is available in a generic formulation. This class was last reviewed in November 2009.

Table 1. Pyrimidines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Flucytosine	capsule	Ancobon®*	flucytosine

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

The pyrimidines 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 FDA-approved indications for the pyrimidines 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 anti-infective 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 Pyrimidines[1-3]

Organism	Flucytosine
Cryptococcus species	✔
Candida species	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Pyrimidines

Clinical Guideline	Recommendation(s)
American Thoracic Society (ATS): **Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients[19] (2011)**	Cryptococcosis • In patients with disseminated cryptococcosis or CNS involvement, amphotericin B (0.7–1.0 mg/kg/d) plus flucytosine (100 mg/kg/d) is recommended for 2 weeks, then fluconazole or itraconazole (400 mg/d) for 8 to 10 weeks. • Alternatively, amphotericin B (0.7–1.0 mg/kg/d) plus flucytosine (100 mg/kg/d) may be administered for 6 to 10 weeks in patients in whom azoles cannot be used.
Infectious Diseases Society of	Candida Endophthalmitis

Clinical Guideline	Recommendation(s)
America (IDSA): **Clinical Practice Guidelines for the Management of Candidiasis[5] (2009)**	• Amphotericin B deoxycholate (AmB-d) combined with flucytosine is recommended for advancing lesions or lesions threatening the macula. Fluconazole is an acceptable alternative for less severe endophthalmitis. Amphotericin B lipid formulation (LFAmB), voriconazole, or an echinocandin can be used to treat patients who are intolerant of or experiencing treatment failure with AmB-d in combination with flucytosine or fluconazole. Cardiovascular Candida Infections • For native valve endocarditis, LFAmB with or without flucytosine is recommended. Alternatives include AmB-d with or without flucytosine or an echinocandin (caspofungin or anidulafungin). Step-down therapy to fluconazole should be considered among patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. Valve replacement is recommended, and treatment should continue for at least 6 weeks after valve replacement and should continue for a longer duration in patients with perivalvular abscesses and other complications. • For patients who cannot undergo valve replacement, long-term suppression with fluconazole is recommended. • For prosthetic valve endocarditis (PVE), the recommendations above apply, and suppressive therapy should be lifelong if valve replacement is not possible. • For myocarditis, treatment as for endocarditis is recommended. • For pacemaker and implantable cardiac defibrillator wire infections, removal of the entire device and systemic antifungal therapy with LFAmB with or without flucytosine, AmB-d with or without flucytosine, or an echinocandin is recommended. Step-down therapy to fluconazole should be considered for patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. For infections limited to generators and/or pockets, 4 weeks of antifungal therapy after removal of the device is recommended. For pacemaker and implantable cardiac defibrillator wire infections, at least 6 weeks of antifungal therapy after wire removal is recommended. Central Nervous System Candidiasis • LFAmB with or without flucytosine is recommended for the initial several weeks of treatment. • Fluconazole is recommended as step-down therapy after the patient responds to initial treatment with LFAmB and flucytosine. Therapy should continue until all signs and symptoms, CSF abnormalities, and radiologic abnormalities have resolved. Urinary Tract Infections – Symptomatic Candiduria • For cystitis due to a fluconazole-susceptible *Candida* species, oral fluconazole for 2 weeks is recommended. For fluconazole-resistant organisms, AmB-d for 1–7 days or oral flucytosine for 7–10 days are alternatives. • For pyelonephritis due to fluconazole-susceptible organisms, oral fluconazole daily for 2 weeks is recommended. For patients with fluconazole-resistant *Candida* strains, especially *C. glabrata*, alternatives include AmB-d with or without flucytosine, or flucytosine alone for 2 weeks. • For fungus balls, surgical intervention is strongly recommended in non-neonates. Fluconazole is recommended. AmBd with or without flucytosine is an alternative. If access to the renal collecting system is available, an adjunct to systemic therapy is irrigation with AmB-d. Treatment duration should be until symptoms have resolved.

Clinical Guideline	Recommendation(s)

Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for the Management of Cryptococcal Disease[6] (2010)**	<u>Cryptococcal Meningoencephalitis (HIV-Infected Individuals)</u>
	• Primary therapy: induction and consolidation:
	  ○ Amphotericin B (AmB) deoxycholate (AmBd) (0.7–1.0 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses; IV formulations may be used in severe cases and in those without oral intake where the preparation is available) for at least 2 weeks, followed by fluconazole (400 mg [6 mg/kg] per day orally) for a minimum of 8 weeks.
	  ○ Lipid formulations of AmB (LFAmB), including liposomal AmB (3–4 mg/kg per day IV) and AmB lipid complex (ABLC) (5 mg/kg per day IV) for at least 2 weeks, could be substituted for AmBd among patients with or predisposed to renal dysfunction.
	• Alternative regimens for induction and consolidation (listed in order of highest recommendation top to bottom):
	  ○ AmBd (0.7–1.0 mg/kg per day IV), liposomal AmB (3–4 mg/kg per day IV), or ABLC (5 mg/kg per day IV) for 4–6 weeks. Liposomal AmB has been given safely at 6 mg/kg per day IV in cryptococcal meningoencephalitis and could be considered in the event of treatment failure or high–fungal burden disease.
	  ○ AmBd (0.7 mg/kg per day IV) plus fluconazole (800 mg per day orally) for 2 weeks, followed by fluconazole (800 mg per day orally) for a minimum of 8 weeks.
	  ○ Fluconazole (≥800 mg per day orally; 1200 mg per day is favored) plus flucytosine (100 mg/kg per day orally) for 6 weeks.
	  ○ Fluconazole (800–2000 mg per day orally) for 10–12 weeks; a dosage of ≥1200 mg per day is encouraged if fluconazole alone is used.
	  ○ Itraconazole (200 mg twice per day orally) for 10–12 weeks, although use of this agent is discouraged.
	<u>Non-Meningeal, Pulmonary Cryptococcosis (Immunosuppressed):</u>
	• For mild-to-moderate symptoms, absence of diffuse pulmonary infiltrates, absence of severe immunosuppression, and negative results of a diagnostic evaluation for dissemination, use fluconazole (400 mg [6 mg/kg] per day orally) for 6–12 months.
	• In HIV-infected patients who are receiving HAART with a CD4 cell count >100 cells/µL and a cryptococcal antigen titer that is ≤1:512 and/or not increasing, consider stopping maintenance fluconazole after 1 year of treatment.
	<u>Cryptococcal Meningoencephalitis (Non–HIV-Infected, Non-transplant)</u>
	• AmBd (0.7–1.0 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for at least 4 weeks for induction therapy. The 4-week induction therapy is reserved for persons with meningoencephalitis without neurological complications and cerebrospinal fluid (CSF) yeast culture results that are negative after 2 weeks of treatment. For AmBd toxicity issues, LFAmB may be substituted in the second 2 weeks. In patients with neurological complications, consider extending induction therapy for a total of 6 weeks, and LFAmB may be given for the last 4 weeks of the prolonged induction period. Then, start consolidation with fluconazole (400 mg per day) for 8 weeks.
	• If patient is AmBd intolerant, substitute liposomal AmB (3–4 mg/kg per day IV) or ABLC (5 mg/kg per day IV).
	• If flucytosine is not given or treatment is interrupted, consider

Clinical Guideline	Recommendation(s)
	lengthening AmBd or LFAmB induction therapy for at least 2 weeks. • In patients at low risk for therapeutic failure, consider induction therapy with combination of AmBd plus flucytosine for only 2 weeks, followed by consolidation with fluconazole (800 mg [12 mg/kg] per day orally) for 8 weeks. • After induction and consolidation therapy, use maintenance therapy with fluconazole (200 mg [3 mg/kg] per day orally) for 6–12 months. <u>Non-Meningeal, Pulmonary Cryptococcosis (Non-Immunosuppressed):</u> • For mild-to-moderate symptoms, administer fluconazole (400 mg per day orally) for 6–12 months; persistently positive serum cryptococcal antigen titers are not criteria for continuance of therapy. • For severe disease, treat similarly to CNS disease. • Itraconazole (200 mg twice per day orally), voriconazole (200 mg twice per day orally), and posaconazole (400 mg twice per day orally) are acceptable alternatives if fluconazole is unavailable or contraindicated. <u>Organ Transplant Recipients</u> • For central nervous system (CNS) disease, liposomal AmB (3–4 mg/kg per day IV) or ABLC (5 mg/kg per day IV) plus flucytosine (100 mg/kg per day in 4 divided doses) for at least 2 weeks for the induction regimen, followed by fluconazole (400–800 mg [6–12 mg/kg] per day orally) for 8 weeks and by fluconazole (200–400 mg per day orally) for 6–12 months. If induction therapy does not include flucytosine, consider LFAmB for at least 4–6 weeks of induction therapy, and liposomal AmB (6 mg/kg per day) might be considered in high–fungal burden disease or relapse. • For mild-to-moderate non-CNS disease, fluconazole (400 mg [6 mg/kg] per day) for 6–12 months. • For moderately severe–to-severe non-CNS or disseminated disease without CNS involvement, treat the same as CNS disease. • In the absence of any clinical evidence of extrapulmonary or disseminated cryptococcosis, severe pulmonary disease is treated the same as CNS disease. For mild-to-moderate symptoms without diffuse pulmonary infiltrates, use fluconazole (400 mg [6 mg/kg] per day) for 6–12 months. • Fluconazole maintenance therapy should be continued for at least 6–12 months. <u>Cryptococcal Meningoencephalitis (Management of Complications - Persistence)</u> • Reinstitute induction phase of primary therapy for longer course (4–10 weeks). • Consider increasing the dose if the initial dosage of induction therapy was ≤0.7 mg/kg IV of AmBd per day or ≤3 mg/kg of LFAmB per day, up to 1 mg/kg IV of AmBd per day or 6 mg/kg of liposomal AmB per day; in general, combination therapy is recommended. • If the patient is polyene intolerant, consider fluconazole (≥800 mg per day orally) plus flucytosine (100 mg/kg per day orally in 4 divided doses). • If patient is flucytosine intolerant, consider AmBd (0.7 mg/kg per day IV) plus fluconazole (800 mg [12 mg/kg] per day orally). • Use of intrathecal or intraventricular AmBd is generally discouraged and is rarely necessary. <u>Cerebral Cryptococcomas</u> • Induction therapy with AmBd (0.7–1 mg/kg per day IV), liposomal AmB (3–4 mg/kg per day IV), or ABLC (5 mg/kg per day IV) plus

Clinical Guideline	Recommendation(s)
	flucytosine (100 mg/kg per day orally in 4 divided doses) for at least 6 weeks. • Consolidation and maintenance therapy with fluconazole (400–800 mg per day orally) for 6–18 months. Non-Meningeal, Non-Pulmonary Cryptococcosis • If CNS disease is ruled out, fungemia is not present, infection occurs at single site, and there are no immunosuppressive risk factors, consider fluconazole (400 mg [6 mg/kg] per day orally) for 6–12 months.
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[15] (2008)**	Cryptococcosis • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the CSF but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a 2-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for 8 weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the pyrimidines 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 Pyrimidines[1-3]

Indication	Flucytosine
Treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus* in combination with amphotericin B	✔

IV. Pharmacokinetics

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

Table 5. Pharmacokinetic Parameters of the Pyrimidines[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Flucytosine	80-90	<4	Not reported	Renal (65-90)	3-8

V. Drug Interactions

No significant drug interactions have been reported with the pyrimidines.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the pyrimidines are listed in Table 6. The boxed warning for flucytosine is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Pyrimidines[1-3]

Adverse Events	Flucytosine
Cardiovascular System	
Cardiac arrest	✔
Chest pain	✔
Myocardial toxicity	✔
Ventricular dysfunction	✔
Central Nervous System	
Ataxia	✔
Confusion	✔
Dizziness	✔
Drowsiness	✔
Fatigue	✔
Hallucinations	✔
Headache	✔
Paresthesia	✔
Parkinsonism	✔
Peripheral neuropathy	✔
Psychosis	✔
Pyrexia	✔
Sedation	✔
Seizure	✔
Vertigo	✔
Dermatological	
Photosensitivity	✔
Pruritus	✔
Rash	✔
Toxic epidermal necrolysis	✔
Urticaria	✔
Gastrointestinal	
Abdominal pain	✔
Anorexia	✔
Diarrhea	✔
Dry mouth	✔
Duodenal ulcer	✔
Gastrointestinal hemorrhage	✔
Nausea	✔
Ulcerative colitis	✔
Vomiting	✔
Genitourinary	
Azotemia	✔
Crystalluria	✔
Renal failure	✔

Adverse Events	Flucytosine
Hematological	
Agranulocytosis	✔
Anemia	✔
Aplastic anemia	✔
Eosinophilia	✔
Leukopenia	✔
Pancytopenia	✔
Thrombocytopenia	✔
Hepatic	
Acute hepatic injury	✔
Hepatic dysfunction	✔
Jaundice	✔
Laboratory Test Abnormalities	
Bilirubin increased	✔
BUN increased	✔
Hypoglycemia	✔
Hypokalemia	✔
Liver enzymes increased	✔
Serum creatinine increased	✔
Respiratory	
Dyspnea	✔
Respiratory arrest	✔
Other	
Allergic reactions	✔
Hearing loss	✔
Weakness	✔

✔ Percent not specified

Table 7. Boxed Warning for Flucytosine[1]

WARNING
Use with extreme caution in patients with impaired renal function. Close monitoring of hematologic, renal and hepatic status of all patients is essential.

VII. Dosing and Administration

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

Table 8. Usual Dosing Regimens for the Pyrimidines[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Flucytosine	*Candida* or *Cryptococcus* Infections: 50 to 150 mg/kg/day administered in divided doses every 6 hours	Safety and efficacy in children have not been established.	Capsule: 250 mg 500 mg

VIII. Effectiveness

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

Table 9. Comparative Clinical Trials with the Pyrimidines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Candidiasis				
Abele-Horn et al.[7] (1996) Flucytosine 3×2.5 g as a total daily dose plus amphotericin B 1 to 1.5 mg/kg/day every other day for 14 days vs fluconazole 400 mg IV on day 1, then 200 mg daily for 14 days	MC, PRO, RCT Patients 18-80 years of age in the intensive care unit with evidence of systemic *Candida* infection	N=72 14 days	Primary: Clinical response (cure=resolution of all symptoms and signs of infection), microbiological response (cure=eradication of *Candida* species)	Primary: No significant differences were seen between the treatment groups in the treatment of pneumonia and sepsis/fungemia. In the treatment of peritonitis, amphotericin B plus flucytosine was more effective than fluconazole, as seen in clinical and microbiological response (P<0.05).
Kujath et al.[8] (1993) Flucytosine 3×2.5 g as a total daily dose plus amphotericin B 0.5 mg/kg/day vs fluconazole 400 mg IV on day 1 then 300 mg daily	OL, PRO, RCT Patients ≥18 years of age with systemic candidiasis	N=40 Variable duration	Primary: Microbiological response (elimination or improvement [reduction of fungal density by 2 stages on a 6-stage scale]), time to elimination of all fungi	Primary: No statistical difference was observed between groups in microbiological elimination or improvement (P=0.44). Fungal elimination was observed significantly sooner in the amphotericin B plus flucytosine group compared to the fluconazole group (5.5 days and 8.5 days, respectively; P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cryptococcal Disease				
van der Horst et al.[9] (1997) Step 1 Flucytosine 100 mg/kg/day plus amphotericin B (0.7 mg/kg/day) in four divided doses for 2 weeks vs amphotericin B (0.7 mg/kg/day) for 2 weeks Step 2 Fluconazole 800 mg oral loading dose, then 400 mg orally daily for 8 weeks vs itraconazole 600 mg oral loading dose daily for 3 days, followed by 200 mg 2 times daily for 8 weeks	DB, MC, RCT Patients ≥13 years of age with HIV infection and a first episode of cryptococcal meningitis confirmed by cerebrospinal fluid culture	N=381 10 weeks	Primary: Mycological outcome (CSF culture negative at weeks 2 and 10), clinical outcome (fever, headache, meningismus improved at week 2 and absent at week 10)	Primary: At week 2 (end of step 1), 60% of patients in the amphotericin B plus flucytosine group had negative cultures compared to 51% of patients in the amphotericin B monotherapy group (P=0.06). At week 2, there was no significant difference between groups in the proportion of patients with stable or improved symptoms, unchanged or improved Mini-Mental State Exam, or combined mycological and clinical responses (P>0.12). At week 10 (end of step 2), there were no significant differences between groups in the clinical or mycological efficacy.
Brouwer et al.[10] (2004)	RCT Adult patients with	N=64 10 weeks	Primary: Fungicidal activity (rate of reduction	Primary: Early fungicidal activity was significantly greater in the amphotericin B plus flucytosine group compared to the other 3 groups (P<0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Flucytosine 100 mg/kg/day plus amphotericin B 0.7 mg/kg/day for 2 weeks vs flucytosine 100 mg/kg/day plus amphotericin B 0.7 mg/kg/day plus fluconazole 400 mg daily for 2 weeks vs amphotericin B 0.7 mg/kg/day for 2 weeks vs amphotericin B 0.7 mg/kg/day plus fluconazole 400 mg daily for 2 weeks After 2 weeks, all patients were treated with fluconazole 400 mg daily for 8 weeks, followed by 200 mg daily.	HIV infections and a first episode of cryptococcal meningitis		in CSF cryptococcal colony-forming units [CFU] from sequential CSF cultures on days 3, 7, and 14 of treatment)	

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chotmongkol et al.[11] (1997) Flucytosine 150 mg/kg/day plus amphotericin B 0.3 mg/kg/day plus itraconazole 400 mg/day (study group) vs flucytosine 150 mg/kg/day plus amphotericin B 0.3 mg/kg/day (control group)	OL, RCT Patients with AIDS and a diagnosis of cryptococcal meningitis	N=100 6 weeks	Primary: Clinical treatment outcomes, mean length of time until normalization of body temperature, mean time until negative CSF culture	Primary: Successful treatment was significantly higher in the study group compared to the control group (100% and 90%, respectively; P=0.03). Mean length of time until normal body temperature was shorter in the study group compared to the control group (5.9 days and 8.8 days, respectively; P=0.02). The mean length of time until the first negative CSF culture was 13.9 days in the study group and 13.3 days in the control group (P=0.66). Relapse rates were higher in the study group.
Bennett et al.[12] (1979) Flucytosine 150 mg/kg/day divided every 6 hours plus amphotericin B 0.3 mg/kg/day for 6 weeks vs amphotericin B 0.4 mg/kg/day for 42 days, then 0.8 mg/kg every other day for 28 days	PRO, RCT Patients with either positive CSF smear or culture or clinical features compatible with cryptococcal meningitis plus a positive culture from another site or positive cryptococcal antigen test or evidence of intracranial cryptococcosis	N=78 10 weeks	Primary: Cure rates and mortality	Primary: Cure or improvement was observed in 66% of patients in the combination group and in 47% of patients in the amphotericin B group (P>0.05). There were 15 deaths in the amphotericin B group (47%) compared to 8 deaths in the combination group (24%; P<0.05).
Larsen et al.[13]	PRO, RCT	N=26	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1990) Flucytosine 150 mg/kg/day in 4 divided doses for 10 weeks plus amphotericin B 0.7 mg/kg/day for 7 days, then 3 times weekly for 9 weeks vs fluconazole 400 mg orally for 10 weeks	Patients ≥18 years of age with evidence of cryptococcal meningitis (with or without AIDS)	62 weeks	Clinical outcomes (success=negative blood and CSF cultures)	After 10 weeks of treatment, 8 of 14 patients receiving fluconazole were considered failures, while 0 of 6 patients taking amphotericin B plus flucytosine were considered failures (P=0.04). Conversion from positive to negative blood and CSF cultures was significantly slower in patients taking fluconazole compared to amphotericin B and flucytosine for CSF cultures (P=0.02). No significant difference was seen in the time to achieve mycological success for blood cultures (P=0.19).
de Gans et al.[14] (1992) Flucytosine 150 mg/kg/day in 4 divided doses plus amphotericin B 0.3 mg/kg/day for 6 weeks vs itraconazole 200 mg twice daily for 6 weeks All patients received itraconazole 200 mg/day as	OL, PRO, RCT Patients with suspected cryptococcal meningitis	N=28 6 weeks	Primary: Response to therapy (complete= resolution of symptoms and negative CSF cultures, partial= resolution of symptoms with persistently positive cultures), survival, relapse rates	Primary: Five of 14 patients in the itraconazole group showed a complete response and 7 showed a partial response. Twelve of 14 patients in the itraconazole group survived for more than 6 weeks. Ten of 11 patients in the amphotericin B and flucytosine group had a complete response. Ten of 11 patients in the amphotericin B and flucytosine group survived for more than 6 weeks. The difference in complete response between groups was significant and favored the amphotericin B and flucytosine group (P=0.009). Overall, no significant difference in relapse rates was observed between original groups during the maintenance period (P=0.22). No significant difference in mean survival was observed between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
maintenance therapy.				original treatment groups (P=0.65).
Bicanic et al.[17] (2008) Group 1 Flucytosine 25 mg/kg divided 4 times daily plus amphotericin B deoxycholate 0.7 mg/kg/day for 2 weeks vs Group 2 Flucytosine 25 mg/kg divided 4 times daily plus amphotericin B 1 mg/kg per day for 2 weeks After 2 weeks, patients received fluconazole 400 mg/day for 8 weeks and 200 mg/day thereafter.	RCT HIV-infected adults hospitalized with a first episode of cryptococcal meningitis	N=64 10 weeks	Primary: Mean rate of decrease in the number of *Cryptococcus* colony-forming units in the cerebrospinal fluid (CSF) or early fungicidal activity (EFA) Secondary: Rates of renal impairment and anemia, mortality at 2 and 10 weeks, and long-term survival during antiretroviral therapy	Primary: The rate of clearance of infection during the first 2 weeks of therapy was more rapid for group 2 than for group 1. The mean EFA was -0.56 log cfu/mL of CSF per day for group 2 and -0.45 log cfu/mL of CSF per day for group 1. Secondary: The mortality rate was 6% at 2 weeks and 24% at 10 weeks, with no difference between groups. Sixty-eight percent and 60% of patients were alive at 6 months and 1 year, respectively, of follow-up. There was no difference in survival rates between the 2 groups at any time point. There were no significant differences between groups 1 and 2 in measurements of renal impairment. A decrease in the hemoglobin level 12 g/dL developed in 50% and 71% of patients in groups 1 and 2, respectively (P=0.2). The percentage decrease in the hemoglobin level was greater for group 2 (95% CI, 2%–15%; P=0.01) and greater for women (95% CI, 4%–17%; P=0.002).
Milefchik et al.[4] (2008) Cohort 1 Fluconazole 800 mg for 10 weeks	RCT HIV-infected adults with a first episode of cryptococcal meningitis	N=89 10 weeks	Primary: Overall response rates (success defined as alive and cerebrospinal fluid [CSF] culture	Primary: Fluconazole alone at the highest doses (1,600 mg and 2,000 mg/day) had clinical success rates of 62%. As the dose level of fluconazole was increased, there was an incremental increase in response (P<0.02). At each dose level of fluconazole (except 1,600 mg dosing of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
with or without flucytosine 100 mg/kg/day for 4 weeks Cohort 2 Fluconazole 1,200 mg for 10 weeks with or without flucytosine 100 mg/kg/day for 4 weeks Cohort 3 Fluconazole 1,600 mg for 10 weeks with or without flucytosine 100 mg/kg/day for 4 weeks Cohort 4 Fluconazole 2,000 mg for 10 weeks with or without flucytosine 100 mg/kg/day for 4 weeks			negative)	fluconazole), the addition of flucytosine to the fluconazole improved the overall response rates (P<0.02). There was a two way interaction between the fluconazole and flucytosine with higher doses of fluconazole associated with an improved response and the addition of flucytosine to fluconazole improving response (P<0.05). The overall success was 75% for subjects that received the combination of fluconazole and flucytosine. No relapses were observed during follow-up among those subjects deemed successful at 10 weeks.
Nussbaum et al.[18] (2010) Flucytosine 100 mg/kg/day plus fluconazole 1,200 mg daily, followed by fluconazole 800 mg/day	OL, RCT HIV-positive adults with their first episode of cryptococcal meningitis	N=41 24 days	Primary: Rate of CSF infection clearance	Primary: The rate of clearance of infection was more rapid in the combination arm compared with fluconazole alone. The difference in EFA was 0.18 (95% CI, 0.085 to 0.27; P=0.0005). Four patients in the combination arm and 1 in the monotherapy arm had sterile CSF cultures by day 14.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluconazole 1,200 mg daily for 14 days				
Sloan et al.[16] (2008) Amphotericin B, flucytosine, and fluconazole given alone or in combination	MA HIV-infected adults with a first episode of cryptococcal meningitis	N=595 (5 trials) ≥2 weeks	Primary: Mortality, adverse events, and proportion of patients with sterile cerebrospinal fluid (CSF) after 2 weeks of therapy	Primary: <u>Fluconazole and flucytosine vs fluconazole</u> There was no difference in death rate at two weeks (RR, 0.4; 95% CI, 0.14 to 1.11) or at six months (RR, 0.77; 95% CI, 0.57 to 1.05). There were no major adverse events in either group. There was no difference in number of patients with sterile CSF at 2 months after treatment (RR, 0.4; 95% CI, 0.11 - 1.36). <u>Amphotericin B vs amphotericin B and flucytosine</u> There was no difference in the proportion deaths at 14 days (RR, 1.1; 95% CI, 0.51 to 2.4). There was no difference in major adverse events between the two treatment arms (RR, 0.94; 95% CI, 0.29 to 3.03).There was higher proportion of patients with sterile CSF cultures at 14 days in the group of patients receiving flucytosine (RR, 0.81; 95% CI, 0.68 to 0.98). <u>Amphotericin B vs amphotericin B, flucytosine and fluconazole</u> There was no significant difference in the proportion of patients dying at two weeks or ten weeks (RR, 2.0; 95% CI, 0.2 to 19.91 and RR, 1.0; 95% CI, 0.24 to 4.23, respectively). There were no serious adverse events in either group. There was no difference in the proportion of patients with sterile CSF at 14 days (RR, 0.5; 95% CI, 0.11 to 2.35). <u>Amphotericin B and flucytosine vs amphotericin B, flucytosine and fluconazole</u> There was no difference in death at 14 days or 10 weeks between the groups (RR, 1.07; 95% CI, 0.07 to 15.57 and RR, 1.07; 95% CI, 0.07 to 15.57, respectively). There were no serious adverse events in either group. There was no difference in the proportion of patients with sterile CSF at 14 days (RR, 1.6; 95% CI, 0.56 to 4.58).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Amphotericin B and flucytosine vs amphotericin B and fluconazole There was no difference in the proportion of deaths at 14 days or 10 weeks (RR, 0.21; 95% CI, 0.03 to 1.62 and RR, 0.15; 95% CI, 0.02 to 1.1). There were no serious adverse events in either group. There was no difference in the amount of patients with sterile CSF at 14 days (RR, 2.13 95% CI 0.65 to 7.04). Amphotericin B vs amphotericin B and fluconazole There was no difference in the proportion deaths at 14 days or 10 weeks (RR, 0.4; 95% CI, 0.09 to 1.77 and RR, 0.43; 95% CI, 0.13 to 1.37). There were no serious adverse events in either group. There was no difference in the amount of patients with sterile CSF at 14 days (RR, 0.67; 95% CI, 0.13 to 3.47). Amphotericin B and fluconazole vs amphotericin B, flucytosine and fluconazole There was no difference in the proportion deaths at 14 days or 10 weeks (RR, 5.0; 95% CI, 0.66 to 38.15 and RR, 2.33; 95% CI, 0.73 to 7.45). There were no serious adverse events in either group. There was no difference in the amount of patients with sterile CSF at 14 days (RR, 0.75; 95% CI, 0.2 to 2.83). Standard dose amphotericin B and flucytosine vs high dose amphotericin B and flucytosine There was no difference in the proportion of deaths at 14 days or 10 weeks (RR, 0.34; 95% CI, 0.04 - 3.44 and RR, 0.76; 95% CI 0.03 to 1.83, respectively). There was no difference in major adverse events defined as side effects of treatment leading the study interventions being terminated (RR, 0.23; 95% CI, 0.03 - 1.83). The proportion of patients with sterile CSF at 14 days was not different between the two treatment groups (RR, 1.13; 95% CI, 0.43 - 2.94). Amphotericin B vs liposomal amphotericin B There was no difference in the proportion of patients who had a clinical response after 3 weeks treatment in the liposomal amphotericin B group and the amphotericin B group (RR, 0.95; 95% CI, 0.67 to 1.33). There was no difference in the proportion of deaths at 14 days,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				10 weeks or 6 months. At 6 months 2/15 patients who received liposomal amphotericin B had died and 1/13 patients who received amphotericin B (RR, 1.73; 95% CI, 0.12 - 59.4). Major adverse events were less common in patients who received liposomal amphotericin B (RR, 0.19; 95% CI, 0.05 - 0.74). There was no difference in the patients with sterile CSF at 14 days in either group (RR, 6.0; 95% CI, 0.91 to 39.41).

Drug regimen abbreviations: IV=intravenous
Study abbreviations: DB=double blind, MC=multi-center, OL=open label, PRO=prospective trial, RCT=randomized controlled trial
Miscellaneous abbreviations: AIDS= acquired immunodeficiency syndrome. CSF=cerebrospinal fluid, HIV=human immunodeficiency virus

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 Pyrimidines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Flucytosine	capsule	Ancobon®*	$$$$$	$$$$$

*Generic is available in at least one dosage form or strength.

X. Conclusions

Flucytosine is approved for the treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus*.[1-3] It should be used in combination with amphotericin B because of the emergence of resistance. Flucytosine is available in a generic formulation.

Guidelines recommend the use of amphotericin B, with or without flucytosine, for the treatment of candida endophthalmitis, cardiovascular candidiasis, central nervous system candidiasis, and for the treatment of fluconazole-resistant urinary tract infections.[5] For the treatment of cryptococcal disease, guidelines recommend the combination of amphotericin B and flucytosine in immunocompetent individuals with severe pulmonary disease and central nervous system (CNS) infections.[6] The combination is recommended in organ transplant recipients with CNS infections, moderately severe-to-severe non-CNS or disseminated disease, as well as severe pulmonary disease. Amphotericin B and flucytosine are also recommended for the treatment of HIV-infected individuals with cryptococcal meningoencephalitis.[6,15]

Clinical trials have demonstrated similar efficacy with the combination of flucytosine and amphotericin B compared to fluconazole monotherapy in patients with systemic candidiasis.[7-8] Several trials have also evaluated the use of flucytosine for the treatment of cryptococcal infections with variable results. Two studies demonstrated similar efficacy with the combination of flucytosine and amphotericin B compared to amphotericin B monotherapy.[9,12] Whereas, three other studies demonstrated better clinical outcomes with the combination of flucytosine and amphotericin B compared to monotherapy with amphotericin B, fluconazole or itraconazole.[10,13-14] A meta-analysis of 5 studies found no difference in mortality with flucytosine treatment regimens compared to other antifungal treatment regimens in HIV-infected adults with cryptococcal meningitis.[16]

Therefore, all brand pyrimidines 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 pyrimidine 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antifungals, Miscellaneous
AHFS Class 081492
May 9, 2012

I. Overview

Griseofulvin is approved for the treatment of tinea barbae, tinea capitis, tinea corporis, tinea cruris, tinea pedis and tinea unguium.[1-4] It is fungistatic with activity against *Epidermophyton*, *Microsporum* and *Trichophyton* species. Griseofulvin is supplied in two different formulations, including microsize and ultramicrosize. The gastrointestinal absorption of ultramicrosize griseofulvin is approximately one and one-half times that of microsize griseofulvin.[4] This allows for the administration of lower doses with the ultramicrosize product; however, there is currently no evidence that this lower dose confers any significant clinical differences with regardd to efficacy or safety.[4]

The miscellaneous antifungals that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The topical antifungals were previously reviewed with the skin and mucous membrane agents (AHFS 840408) and are not included in this review. Griseofulvin microsize suspension is available in a generic formulation. This class was last reviewed in November 2009.

Table 1. Antifungals, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Griseofulvin microsize	suspension, tablet	Grifulvin V®	griseofulvin microsize
Griseofulvin ultramicrosize	tablet	Gris-Peg®	Gris-Peg®

PDL=Preferred Drug List

The miscellaneous antifungals 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 FDA-approved indications for the miscellaneous antifungals 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 anti-infective 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 Antifungals, Miscellaneous[1-4]

Organism	Griseofulvin Microsize	Griseofulvin Ultramicrosize
Epidermophyton floccosum	✔	✔
Microsporum audouinii	✔	✔
Microsporum canis	✔	✔
Microsporum gypseum	✔	✔
Trichophyton crateriform	✔	✔
Trichophyton gallinae	✔	✔
Trichophyton interdigitalis	✔	✔
Trichophyton megninii	✔	✔
Trichophyton mentagrophytes	✔	✔
Trichophyton rubrum	✔	✔
Trichophyton schoenleinii	✔	✔
Trichophyton sulphureum	✔	✔
Trichophyton tonsurans	✔	✔
Trichophyton verrucosum	✔	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Antifungals, Miscellaneous

Clinical Guideline	Recommendation(s)
European Academy of Dermatology and Venereology (EADV): **Onychomycosis Treatment Guidelines[6] (2005)**	• Prior to initiating treatment, it is important that diagnosis be confirmed and the etiological agent identified. • Topical monotherapy is indicated when the matrix area is not involved. Topical treatment is also suitable for patients who are reluctant to take oral medications or have swallowing difficulties. The only case in which it is not recommended is if nail penetration may be suboptimal. • Oral antifungal drugs are generally considered to be more effective than topical treatments. However, they are accompanied by a higher risk of systemic adverse effects and drug interactions. • Oral monotherapy (terbinafine, itraconazole or fluconazole) or combined oral and topical (nail lacquer) is recommended when 1) at least 50% of the distal nail plate is involved; 2) the nail matrix area is involved; 3) mycological criteria such as the causative agent or agents are known and oral agents can target specific fungi; 4) topical drugs are not indicated when topical drug transport is suboptimal; and 5) oral or combined therapy is also recommended in cases of nail matrix area involvement. • Griseofulvin is associated with the poorest mycological cure rate (<30%) and is rarely used. Terbinafine is associated with the highest mycological cure rate (77–100%).
British Association of Dermatologists (BAD): **Guidelines for the Treatment of Onychomycosis[7] (2003)**	• Both topical and oral agents are available for the treatment of fungal nail infection. The primary aim of treatment is to eradicate the organism as demonstrated by microscopy and culture. • Systemic therapy is almost always more successful than topical treatment, which should only be used in superficial white onychomycosis (SWO), possibly very early distal and lateral subungual onychomycosis (DLSO) or when systemic therapy is contraindicated. • Both terbinafine and itraconazole have been shown to be more effective than griseofulvin in dermatophyte onychomycosis and therefore the optimum choice of treatment lies between terbinafine and itraconazole.
European Society for Pediatric Dermatology (ESPD): **Guidelines for the Management of Tinea Capitis in Children[5] (2010)**	• Tinea capitis always requires systemic treatment because topical antifungal agents do not penetrate the hair follicle. • Topical treatment is only used as adjuvant therapy to systemic antifungals. • Griseofulvin has been the gold standard for systemic therapy of tinea capitis. The main disadvantage of griseofulvin is the long duration of treatment required (6–12 weeks or longer) which may lead to reduced compliance. • The newer oral antifungal agents including terbinafine, itraconazole, and fluconazole appear to have efficacy rates and potential adverse effects similar to those of griseofulvin in children with tinea capitis due to *Trichophyton* species, while requiring much shorter duration of treatment. • Griseofulvin is still the treatment of choice for cases caused by *Microsporum* species. • Adjunctive topical therapies, such as selenium sulfide or ketoconazole shampoos, as well as fungicidal creams or lotions have been shown to decrease the carriage of viable spores responsible for the disease

Clinical Guideline	Recommendation(s)
	contagion and reinfection and may shorten the cure rate with oral antifungals. • The topical fungicidal cream/lotion should be applied to the lesions once daily for a week. The shampoo should be applied to the scalp and hair for 5 minutes twice weekly for 2–4 weeks or three times weekly until the patient is clinically and mycologically cured. The latter in conjunction with 1 week of topical fungicidal cream or lotion application is recommended.

British Association of Dermatologists: **Guidelines for the Management of Tinea Capitis[8] (2000)**	• The aim of treatment is to achieve a clinical and mycological cure as quickly as possible.
	• Oral antifungal therapy is generally needed. Topical treatment alone is not recommended for the management of tinea capitis.
	• Oral therapy options include griseofulvin, terbinafine, itraconazole, fluconazole, and ketoconazole.
	• If there has been no clinical response and signs persist at the end of the treatment period, then the options include:
	  o Increase the dose or duration of the original drug (both griseofulvin and terbinafine have been used successfully and safely at higher doses or for longer courses to clear resistant infections)
	  o Change to an alternative antifungal (e.g. switch from griseofulvin to terbinafine or itraconazole).
	• Symptom-free carriers with light growth/low spore count on culture may be treated with twice weekly selenium or povidone shampoo.
	• The definitive end-point for adequate treatment is not clinical response but mycological cure; therefore, follow-up with repeat mycology sampling is recommended at the end of the standard treatment period and then monthly until mycological clearance is documented. Treatment should, therefore, be tailored for each individual patient according to response.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antifungals 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 Antifungals, Miscellaneous[1-4]

Indication	Griseofulvin Microsize	Griseofulvin Ultramicrosize
Tinea barbae	✔	✔
Tinea capitis	✔	✔
Tinea corporis	✔	✔
Tinea cruris	✔	✔
Tinea pedis	✔	✔
Tinea unguium	✔	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antifungals are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Antifungals, Miscellaneous[1-4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Griseofulvin	Variable	Not reported	Liver	Feces (36)	9-22

V. Drug Interactions

Significant drug interactions with the miscellaneous antifungals are listed in Table 6.

Table 6. Significant Drug Interactions with the Antifungals, Miscellaneous[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Griseofulvin	1	Dienogest	Griseofulvin may increase hepatic metabolism and decrease the pharmacologic effects of dienogest. Menstrual irregularities (spotting, breakthrough bleeding, and amenorrhea) and pregnancy may occur.
Griseofulvin	1	Oral contraceptives	Pharmacologic effects of oral contraceptives may be decreased by griseofulvin. Menstrual irregularities (spotting, breakthrough bleeding) and pregnancy may occur.
Griseofulvin	2	Anticoagulants	The hypoprothrombinemic effect of warfarin may be decreased. Suboptimal anticoagulation with possible exacerbation of the problem being treated can occur.
Griseofulvin	2	Cabazitaxel	Inhibition of CYP3A4 by griseofulvin may increase the metabolic elimination of cabazitaxel. Plasma concentrations and pharmacologic effects cabazitaxel may be decreased by griseofulvin.
Griseofulvin	2	Ulipristal	Induction of CYP3A4 enzymes by griseofulvin may increase the metabolic elimination of ulipristal. Plasma concentrations and pharmacologic effects of ulipristal may be decreased by griseofulvin.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antifungals are listed in Table 7.

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

Adverse Events	Griseofulvin
Central Nervous System	
Dizziness	✔
Fatigue	✔
Headache	✔
Insomnia	✔
Mental confusion	✔
Paresthesia	✔
Dermatological	
Erythema multiforme-like drug reaction	✔
Photosensitivity	✔
Rash	✔
Urticaria	✔
Gastrointestinal	
Diarrhea	✔
Epigastric distress	✔
Gastrointestinal bleeding	✔
Nausea	✔
Oral thrush	✔
Vomiting	✔
Genitourinary	
Nephrosis	✔
Proteinuria	✔
Hematological	
Granulocytopenia	✔
Leukopenia	✔
Other	
Angioneurotic edema	✔
Drug-induced lupus-like syndrome	✔
Hepatotoxicity	✔
Menstrual irregularities	✔

✔ Percent not specified

VII. Dosing and Administration

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

Table 8. Usual Dosing Regimens for the Antifungals, Miscellaneous[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Griseofulvin microsize	Tinea Capitis, Tinea Corporis, Tinea Cruris: Tablet/suspension: 500 mg daily Tinea Pedis, Tinea Unguium: Tablet/suspension: 1 gram daily	Tinea Infections: 30 to 50 pounds: Tablet/suspension: 125 mg to 250 mg daily >50 pounds: Tablet/suspension: 250 mg to 500 mg daily	Suspension: 125 mg/5 ml Tablet: 500 mg
Griseofulvin ultramicrosize	Tinea Capitis, Tinea Corporis, Tinea Cruris: 375 mg as a single dose or in	Tinea Infections: >2 years of age: 35 to 60 pounds: 125 mg to	Tablet: 125 mg 250 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	divided doses Tinea Pedis, Tinea Unguium: 750 mg as a single dose or in divided doses	187.5 mg daily >60 pounds: 187.5 mg to 375 mg daily	

VIII. Effectiveness

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

Table 9. Comparative Clinical Trials with the Antifungals, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tinea Capitis				
Dastghaib et al.[13] (2005) Griseofulvin 15 mg/kg/day for 6 weeks vs fluconazole 5 mg/kg/day for 4 weeks	PRO, RCT, SB Patients with a mycological diagnosis of non-inflammatory tinea capitis	N=40 8 weeks	Primary: Complete cure (negative culture and ≥50% decrease in clinical scores which are based on hair loss, erythema, pruritus, presence of crust and presence of scales), mycological cure	Primary: No significant difference was observed in the proportion of patients infected with *Trichophyton* who experienced complete cure in the griseofulvin and fluconazole groups (76% and 93% respectively, P=0.41). No significant difference was observed in the proportion of patients infected with *Microsporum* who experienced complete cure in the griseofulvin and fluconazole groups (P=0.27). No significant difference was observed between groups in mycological cure rate.
Gupta et al.[20] (2001) Griseofulvin 20 mg/kg/day for 6 weeks vs fluconazole 6 mg/kg/day for 2 weeks vs itraconazole 5 mg/kg/day for 2 weeks	CS, PRO, RCT, SB Patients 6 months of age and older with clinical symptoms and signs of tinea capitis confirmed mycologically	N=200 12 weeks	Primary: Complete clinical (negative culture and no signs and symptoms), mycological cure (negative culture and few residual signs and symptoms)	Primary: Effective therapy (complete clinical and mycological cure or mycological cure) was observed in 92% of patients in the griseofulvin group, 94% in the terbinafine group, 86% in the itraconazole group, and 84% in the fluconazole group. No significant differences were noted at week 12 between treatment groups (P=0.33).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs terbinafine 62.5 mg, 125 mg, or 250 mg daily for 2 weeks				
Tanz et al.[14] (1988) Griseofulvin 10-20 mg/kg/day for 12 weeks vs ketoconazole 3.3-6.6 mg/kg/day for 12 weeks	DB, RCT Patients 2-16 years of age with tinea capitis or mycological evidence of dermatophyte infection of the scalp	N=79 12 weeks	Primary: Clinical response (success=clinical improvement and negative cultures), mycological response, symptom severity score	Primary: Treatment success was observed in 73% of patients in the ketoconazole group and in 96% of patients in the griseofulvin group (P<0.10). There were no significant differences in symptom severity scores between groups (P>0.20). There were no significant differences between groups in mycological response (P<0.90).
Tanz et al.[15] (1985) Griseofulvin 500 mg daily vs ketoconazole 200 mg daily	DB, RCT Children 2-16 years of age with mycologically proven tinea capitis	N=22 6 weeks	Primary: Symptom severity score, mycological response (negative cultures)	Primary: The total severity scores decreased in all patients during the course of the study (P<0.05 compared to baseline) and the decrease was similar between groups (P=0.62). After 6 weeks of therapy, 57% of patients in each group were culture negative.
Gan et al.[16] (1987) Griseofulvin 15 mg/kg/day until clearance of lesions and negative culture or for 6 months	RCT Patients 1-12 years of age with a diagnosis of tinea capitis	N=63 6 months	Primary: Negative cultures, relapse rates	Primary: After 1 month of therapy, fungal cultures were negative in 69% of patients treated with griseofulvin and 29% of patients treated with ketoconazole (P<0.01). This statistical difference persisted throughout the follow-up period. At the end of 12 weeks of therapy, 4% of griseofulvin patients continued to have positive cultures compared to 26% in the ketoconazole group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ketoconazole 5 mg/kg/day until clearance of lesions and negative culture or for 6 months				Seven patients (1 in the griseofulvin group and 6 in the ketoconazole group) reverted to negative samples between the 12th and 26th week of treatment. The median time from initiation of therapy to negative culture was significantly longer in the ketoconazole group compared to the griseofulvin group (8 weeks and 4 weeks respectively, P<0.01). Three patients (1 in the griseofulvin group and 2 in the ketoconazole group) had recurrence of tinea capitis at 4 weeks (2 patients) and at 4 months (1 patient) after discontinuation of therapy.
Lipozencic et al.[17] (2002) Griseofulvin oral suspension 20 mg/kg/day for 12 weeks (open-label) vs terbinafine 125 mg or 250 mg (based on weight) daily for 6, 8, 10, or 12 weeks (blinded as to study duration)	DB, MC, PG, RCT Patients 4 years of age and older diagnosed with tinea capitis clinically confirmed by positive culture for *Microsporum* species	N=134 16 weeks	Primary: Complete cure at the end of study (EOS) defined by negative culture and no residual signs and symptoms Secondary: Effective treatment (negative culture and minimal signs and symptoms), clinical cure (no clinical signs and symptoms), mycological cure (negative microscopy and culture)	Primary: There was no significant difference between any of the terbinafine treatment groups in complete cure at EOS (P=0.12). Higher daily doses of terbinafine (>4.5 mg/kg/day) had a positive effect on complete cure rates at EOS compared to lower doses (<4.5 mg/kg/day) (P=0.048). Open-label, high-dose griseofulvin showed a high rate of complete cure at EOS of 84%. No comparisons were made between griseofulvin group and terbinafine groups. Secondary: At EOS, no significant differences were observed between any of the terbinafine treatment groups in any secondary endpoint (P>0.05). Open-label, high-dose griseofulvin produced effective treatment in 88% of patients, mycological cure in 76%, and clinical cure in 96%. No comparisons were made between the griseofulvin and terbinafine groups.
Fuller et al.[18] (2001)	MC, OL, PG, RCT Patients 2-16 years	N=210 24 weeks	Primary: Clinical response (complete cure=	Primary: No significant differences were observed between groups in clinical response (P>0.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Griseofulvin suspension 10 mg/kg/day for 4 weeks vs terbinafine 62.5 mg or 125 mg daily for 4 weeks All patients were instructed to use selenium sulfide shampoo at least 2 times weekly for the first 2 weeks.	of age with a diagnosis of tinea capitis confirmed by culture		microscopy and culture negative, no residual signs and symptoms; cure= microscopy and culture negative and total symptom score ≤2)	Graphical representation of cure rates shows a numerically higher response to terbinafine at earlier time points. Significantly more children weighing over 20 kg and infected with *Trichophyton* species were rated as cured at week 4 compared to children in the griseofulvin group (36% and 13% respectively, P=0.03).
Caceres-Rios et al.[19] (2000) Griseofulvin (microsize) 125 mg, 250 mg, or 500 mg daily for 8 weeks vs terbinafine 62.5 mg, 125 mg, or 250 mg daily for 4 weeks then 4 weeks of placebo	DB, PRO, RCT Patients 1-14 years of age with a clinical and mycological diagnosis of non-inflammatory tinea capitis	N=50 12 weeks	Primary: Clinical outcomes (complete cure= negative culture and resolution of signs and symptoms; mycological cure= negative mycological findings and slight erythema, desquamation or pruritus)	Primary: At the end of 8 weeks, no significant difference was observed between groups with respect to proportion of patients with negative cultures. At the end of week 12, the proportion of patients with negative cultures decreased in the griseofulvin group and increased or remained steady in the terbinafine group. A significant difference in favor of the terbinafine group was observed (P<0.05). At the end of week 8, the efficacy (as measured by complete cure) of griseofulvin was 76% and 72% for terbinafine. No significant difference between groups was observed. By week 12, the efficacy (as measured by complete cure) of griseofulvin had decreased to 44% and terbinafine had risen to 76% (P<0.05).
Elewski et al.[29] (2008)	2 RCT (pooled), SB, MC	N=1,549 10 weeks	Primary: End-of-study complete cure rate	Primary: The complete cure rate at the end-of-study (week 10) was statistically higher in the terbinafine group (45.1%) compared to the griseofulvin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Griseofulvin suspension 125 mg to 500 mg (10-20 mg/kg) once daily for 6 weeks vs terbinafine granules 125 mg to 250 mg (5-8 mg/kg) once daily for 6 weeks	Children between 4 and 12 years of age with a clinical diagnosis of tinea capitis confirmed by positive potassium hydroxide microscopy at baseline		defined as mycologic cure (negative culture and microscopy) and clinical cure Secondary: End-of-study mycologic cure rate, end-of-study clinical cure rate, and adverse events	group (39.2%; P=0.024) in the pooled analysis. In the individual analyses, terbinafine was more effective than griseofulvin in trial 1 (46.23% vs 34.01%, respectively; P<0.01) but not in trial 2 (43.99% vs 43.46%, respectively; P=0.95). Secondary: The end-of-study mycologic cure rate was higher in the terbinafine group (61.5%) compared to the griseofulvin group (55.5%; P=0.029). In the individual analyses, terbinafine was more effective than griseofulvin in trial 1 (62.29% vs 50.25%; P<.01) but not in trial 2 (60.77% vs 59.92%; P=0.89). The end-of-study clinical cure rate were similar between terbinafine and griseofulvin in the pooled analysis (63% vs 58.8%; P=0.10) as well as in the individual trials (trial 1: 62.77% vs 56.35%; P=0.06; trial 2: 63.27% vs 60.76%; P=0.59). Overall, 51.9% of patients in the terbinafine group and 49.1% of patients in the griseofulvin group reported an adverse event during the study. The incidence of adverse events by organ class was similar in the two treatment groups.
Tey et al.[32] (2011) Griseofulvin vs terbinafine	MA Children and adults with a diagnosis of tinea capitis	N=2,163 (7 trials) Variable duration	Primary: Complete cure rate (defined as the achievement of both clinical and mycological cure) Secondary: Mycological cure rate (defined as the absence of dermatophytes on microscopy and culture), clinical cure rate (defined as the resolution of	Primary: The pooled OR did not significantly favor griseofulvin or terbinafine when all studies were pooled (OR, 1.22; 95% CI, 0.785-1.919; P=0.37). For those studies with *Trichophyton* species being the predominant pathogen, the pooled OR favored terbinafine, but did not reach statistical significance (OR, 1.49; 95% CI, 0.975-2.277; P=0.065). For those studies with *Microsporum* species being the predominant pathogen, the pooled OR significantly favored griseofulvin (OR, 0.408; 95% CI, 0.254-0.656; P<0.001). Griseofulvin was associated with a small number of adverse effects including gastrointestinal symptoms, headache, upper respiratory tract symptoms, and rash. Severe adverse effects did not occur. The most frequent adverse events reported with terbinafine were gastrointestinal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			clinical symptoms and signs), adverse events	symptoms and upper respiratory tract symptoms. One patient developed asymptomatic neutropenia that was reversible after treatment was terminated prematurely.
González et al.[30] (2007) Griseofulvin, terbinafine, itraconazole, fluconazole, ketoconazole	MA Children with normal immunity under the age of 18 who had tinea capitis confirmed by microscopy or growth of dermatophytes in culture or both	N=1,812 (21 trials) 6 to 26 weeks	Primary: The proportion of participants with complete cure (clinical and mycological)	Primary: <u>Terbinafine vs griseofulvin</u> A pooled analysis of the five trials found that the difference in the cure rates between four weeks of terbinafine and eight weeks griseofulvin was not statistically significant (RR 1.11, 95% CI 0.96 to 1.29). <u>Itraconazole vs griseofulvin</u> In the pooled analysis, there was no significant difference in cure rates between itraconazole and griseofulvin (RR 0.94 CI 0.80 to 1.09). <u>Itraconazole vs terbinafine</u> In the pooled analysis, there was no significant difference in cure rates between itraconazole and terbinafine (as treatment of *Trichophyton* species) when used for periods of two to three weeks (RR 0.93, 95% CI 0.72 to 1.19). <u>Ketoconazole vs griseofulvin</u> In the pooled analysis, there was no significant difference in cure rates between ketoconazole and griseofulvin (RR 0.72, 95% CI 0.50 to 1.02). <u>Fluconazole vs griseofulvin</u> In the pooled analysis, there was no significant difference in cure rates between fluconazole and griseofulvin (RR 0.92, 95% CI 0.80 to 1.05). <u>Fluconazole vs terbinafine</u> In one study, the cure rates were found to be similar between fluconazole and terbinafine (RR 0.87, 95% CI 0.75 to 1.01). <u>Fluconazole vs itraconazole</u> In one study, the cure rates were found to be similar between fluconazole and itraconazole (RR 1.00, 95% CI 0.83 to 1.20).
Gupta et al.[31] (2008)	MA Patients with	N=438 (7 trials)	Primary: Effective cure (negative	Primary: In the pooled analysis, the overall mean efficacy of griseofulvin at 4 to 6 weeks post-treatment was 73.4%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Griseofulvin (microsize and ultramicrosize formulations)	mycologically-confirmed tinea capitis	4 to 6 weeks post-treatment	mycology with few remaining visual signs of infection)	When broken down by species, the mean efficacy for *Trichophyton* and *Microsporum* were 67.6% (5 studies, n=396) and 88.1% (2 studies, n=42 patients), respectively. Higher efficacy rates were reported for with the use of higher dosages of griseofulvin.
Tinea Corporis and/or Tinea Cruris				
Faergemann et al.[21] (1997) Griseofulvin 500 mg daily for 25-28 days vs fluconazole 150 mg weekly for 25-28 days Treatment continued for a total of 42 days in patients who were not clinically or mycologically cured at 4 weeks.	DB, MC, PG, RCT Patients 16-83 years of age with signs and symptoms of tinea corporis and/or tinea cruris confirmed by microscopy	N=239 42 days	Primary: Clinical cure and mycological cure	Primary: At visit 3 (days 42-44), clinical cure was observed in 74% of fluconazole patients and 62% of griseofulvin patients (P=0.06). At visit 3 (days 42-44) mycological cure was observed in 78% of fluconazole patients and 80% of griseofulvin patients. At visit 2 (days 25-28), clinical cure was observed in 39% of fluconazole patients and 39% of griseofulvin patients. At visit 2 (days 25-28) mycological cure was observed in 72% of fluconazole patients and 70% of griseofulvin patients.
Voravutinon[22] (1993) Griseofulvin 500 mg daily for 2 weeks vs	CS, DB, RCT Patients with mycologically diagnosed tinea corporis and tinea cruris	N=64 4 week posttreatment follow-up	Primary: Clinical response (clearance of lesions), mycological response (negative culture), relapse rates	Primary: After 2 weeks of therapy, the clinical response was the same in both groups. After 2 weeks of therapy, the mycological response was similar in the two groups (90.3% for terbinafine and 80.7% in the griseofulvin). No significant difference was observed.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
terbinafine 250 mg daily for 2 weeks				At 6 weeks, the mycological cure in the terbinafine group was significantly higher than in the griseofulvin group (87.1% and 54.8% respectively, P<0.05). At 6 weeks, the clinical response was significantly higher in the terbinafine group compared to the griseofulvin group. A higher relapse rate was observed in the griseofulvin group compared to the terbinafine group.
Tinea Pedis				
Roberts et al.[23] (1987) Griseofulvin 1 g daily for up to 8 weeks vs ketoconazole 200 mg daily for up to 8 weeks	RCT Patients with mycologically proven tinea pedis	N=29 8 weeks	Primary: Mycological cure (negative culture)	Primary: At 4 weeks, the mycological cure rate was 33% in the ketoconazole group and 29% in the griseofulvin group. At 8 weeks, the mycological cure rate was 53% in the ketoconazole group and 57% in the griseofulvin group.
Tinea Unguium				
Korting et al.[24] (1993) Griseofulvin ultramicrosize (UMSG) 660 mg daily for up to 18 months vs griseofulvin ultramicrosize (UMSG) 990 mg	OL, RCT Patients with clinically confirmed tinea unguium of the toenails, fingernails, or both	N=109 18 months	Primary: Clinical response (cure=clinical remission with negative culture and microscopy; partial cure=microscopy alone remained positive; marked improvement= minimal clinical involvement of test nail and no	Primary: There was no significant difference in the cure or partial cure rates between the USMG 660 mg, USMG 990 mg, and itraconazole 100 mg groups (6%, 14%, and 19% respectively, P=0.2097). Three was no significant difference in the rates of marked improvement between the USMG 660 mg, USMG 990 mg, and itraconazole 100 mg groups (36%, 44%, and 39% respectively). No significant difference in compliance was observed between groups. Itraconazole was significantly better tolerated compared to both USMG groups (P<0.0322).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for up to 18 months vs itraconazole 100 mg daily for up to 18 months			dermatophyte growth), compliance, adverse effects	
Haugh et al.[28] (2002) Griseofulvin 500 mg or 1,000 mg daily for 3 months or 11 months vs itraconazole 200 mg daily or 400 mg intermittently (for 1 of every 4 weeks) for 3 or 4 months vs terbinafine 250 mg daily for 3 or 6 months vs placebo	MA Patients diagnosed with onychomycosis	N=2,063 3-11 months	Primary: Mycological cure at the end of the studies (negative microscopy or culture) Secondary: Negative microscopy or culture at specified time points	Primary: <u>Terbinafine vs placebo (3 trials)</u> After 12 weeks, a significant advantage in mycological cure rates was seen in favor of the terbinafine group compared to the placebo group. <u>Terbinafine vs itraconazole (4 trials)</u> At the end of the study periods, a statistically significant advantage in achieving negative culture and microscopy was seen in favor of terbinafine compared to itraconazole. No significant differences in tolerability were reported. <u>Terbinafine vs griseofulvin (2 trials)</u> A significantly higher rate of negative microscopy and culture were observed in the terbinafine groups at week 24 compared to the griseofulvin groups.
Haneke et al.[25] (1995)	DB, MC, RCT Patients 18 years of	N=180 1 year	Primary: Clinical response (outgrowth from	Primary: Mycological cure rates increased in both groups during active treatment and continued in the terbinafine group during follow-up while remaining

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Griseofulvin microsize 500 mg daily for 12 weeks vs terbinafine 250 mg daily for 12 weeks After 12 weeks of treatment, all patients received an additional 12 weeks of placebo followed by 6 months follow-up.	age and older with clinically confirmed distal subungual onychomycosis of the fingernails		the border of healthy and infected nails), mean global score (based on onycholysis, hyperkeratosis, brittleness, and paronychial inflammation, mycological cure (negative culture), mean time to negative culture	steady in the griseofulvin group. At week 24, 90% of patients in the terbinafine group and 64% in the griseofulvin group were mycologically cured. At the end of the study, 92% of patients in the terbinafine group and 63% in the griseofulvin group were mycologically cured (P<0.001). Mean time to negative culture was 73 days in the terbinafine group and 93 days in the griseofulvin group. The length of unaffected nail increased in the terbinafine group from 3.2 mm to 11.4 mm (week 24) and 12.4 mm (end of study). In the griseofulvin group, it increased from 2.6 mm to 9.5 mm (week 24) and decreased to 8.7 mm at the end of the study (P=0.006 between groups at the end of the study). The mean global scores decreased in the terbinafine group from 5.8 to 0.9 (week 24) and 0.4 (end of study). In the griseofulvin group, the scores decreased from 5.7 to 1.8 (week 24) and increased to 2.2 at the end of the study (P=0.028 at week 24, P<0.001 at end of study).
Faergemann et al.[26] (1995) Griseofulvin 500 mg daily for 52 weeks vs terbinafine 250 mg daily for 16 weeks Patients who did not respond after 16 weeks were	DB, PG, RCT Adult patients with culture-proven tinea of the toenails	N=89 52 weeks	Primary: Complete cure (no signs and symptoms of infection and negative culture), mycological cure (negative culture)	Primary: Significantly more patients in the terbinafine group were completely cured (42%) compared to the griseofulvin group (2%) at the end of the study (P<0.0005). Significantly more patients in the terbinafine group experienced mycological cure (84%) compared to the griseofulvin group (45%) at the end of the study (P<0.0005). Of the patients who switched to open-label treatment with terbinafine, 44% were cured at the end of the study (week 52 or 20 weeks after cessation of open-label terbinafine) compared to 18% in the griseofulvin group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
switched to OL terbinafine for 16 to 20 weeks of follow-up.				
Hoffman et al.[27] (1995) Griseofulvin micronized 1,000 mg daily for 48 weeks vs terbinafine 250 mg daily for 24 weeks followed by 24 weeks of placebo	DB, RCT Patients 21-93 years of age with clinically confirmed distal subungual onychomycosis of the toenails	N=195 72 weeks	Primary: Mycological cure (negative culture), clinical response (global score based on growth of unaffected nail and presence of onycholysis, hyperkeratosis, brittleness, and paronychial inflammation), time to mycological cure	Primary: Mycological cure increased during active therapy in both groups, and slightly decreased in the terbinafine group while sharply decreasing in the griseofulvin group during the follow-up period. At week 48, 88% of terbinafine patients and 82% of griseofulvin patients had negative cultures, while these numbers decreased to 81% and 62% respectively at the end of the study (P=0.02). The time to negative culture was 130 days in the terbinafine group and 172 days in the griseofulvin group (P=0.036). The mean global score in the terbinafine group decreased from 6.3 to 1.4 at week 48 and 0.8 at the end of the study, compared to 7.0 in the griseofulvin group decreasing to 1.7 at week 48 and 1.8 at the end of the study (P=0.010).
General Dermatophyte Infections				
Jolly et al.[9] (1983) Griseofulvin ultramicrosize 250 mg daily for 2-16 weeks vs ketoconazole 200 mg daily for 2-16 weeks	DB, RCT Patients with mycologically confirmed dermatophyte infections	N=137 16 weeks	Primary: Clinical response and mycological response	Primary: Clinical response was observed in 20 of 21 patients in the ketoconazole group compared to 9 of 11 in the griseofulvin group. Mycological response was better in the ketoconazole group compared to the griseofulvin group. In the ketoconazole group, 61% achieved remission compared to 39% in the griseofulvin group (P=0.02). In the ketoconazole group, 9% of patients relapsed compared to 43% in the griseofulvin group (P<0.01).
Stratigos et al.[10] (1983)	DB, RCT Patients with	N=50 6 weeks	Primary: Cure rate (no symptoms and	Primary: After 2 weeks of treatment, 50% of patients in the ketoconazole group vs 25% in the griseofulvin group had negative cultures and this difference

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Griseofulvin 500 mg daily until negative culture or 6 weeks vs ketoconazole 200 mg daily until negative culture or 6 weeks	clinical symptoms and cultures for dermatophytes		negative culture results)	was not statistically significant between groups. At 3 weeks, 88.5% of patients in the ketoconazole group vs 66.6% in the griseofulvin group had negative cultures and this difference was not statistically significant between groups. There was no significant difference in cure rates between groups.
Legendre et al.[11] (1980) Griseofulvin ultramicrosize 250 mg daily for 28-60 days vs ketoconazole 200 mg daily for 28-60 days	DB, RCT Patients with microscopically confirmed dermatophyte infection of the skin	N=58 28 day posttreatment follow-up	Primary: Response to therapy (cure=clearance of lesions and negative culture), relapse rates	Primary: Cure was obtained in 38% of patients in the ketoconazole group and 24% of patients in the griseofulvin group after 4 weeks of therapy. After 60 days of therapy, cure was obtained in 83% of ketoconazole patients and 32% of griseofulvin patients (P<0.001). Of the patients cured after 4 weeks of treatment, none of the ketoconazole patients relapsed and all of the griseofulvin patients relapsed (P=0.001). Of all the patients cured regardless of duration of therapy, 7% of ketoconazole patients relapsed within 28 days compared to 80% in the griseofulvin group (P=0.006).
Martinez-Roig et al.[12] (1988) Griseofulvin 350 mg daily divided every 12 hours until lesions had cleared and negative culture was obtained vs	DB, RCT Patients 3 months to 14 years of age with dermatophyte infections who had not received previous antifungal therapy	N=47 2 week posttreatment follow-up	Primary: Response to therapy (clinical cure= clearance of lesions and mycological cure= negative culture), time to clinical cure and negative culture	Primary: After 6 weeks of therapy, clinical and mycological cure or improvement was seen in 92% of patients treated with ketoconazole and 76% of patients treated with griseofulvin. The time to clinical cure and negative cultures was shorter for patients treated with ketoconazole compared to griseofulvin for tinea capitis, and shorter for griseofulvin compared to ketoconazole for tinea corporis, though no significant difference was observed in overall response to therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ketoconazole 100 mg daily divided every 12 hours until lesions had cleared and negative culture was obtained				

Study abbreviations: CS=comparative study, DB=double blind, DD=double dummy, MA=meta-analysis, MC=multi-center, OL=open label, PG=parallel group, PRO=prospective trial, RCT=randomized controlled trial, 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 Antifungals, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Griseofulvin microsize	suspension, tablet	Grifulvin V®	$$$$	$$
Griseofulvin ultramicrosize	tablet	Gris-Peg®	$$$	N/A

N/A=Not available

X. Conclusions

Griseofulvin is approved for the treatment of tinea barbae, tinea capitis, tinea corporis, tinea cruris, tinea pedis and tinea unguium (onychomycosis).[1-4] It is available in two formulations (microsize and ultramicrosize), which differ in their pharmacokinetic properties. This allows for the administration of lower doses with the ultramicrosize products; however, there is currently no evidence that this lower dose confers any significant clinical differences with regards to efficacy or safety.[4] Griseofulvin microsize suspension is the only product that is available in a generic formulation.

For the treatment of onychomycosis, guidelines recommend the use of systemic antifungals as they are generally more effective than topical treatments.[6-7] Oral monotherapy or combined oral/topical therapy is recommended as initial therapy.[6] Terbinafine should be considered as a first-line treatment option and itraconazole may be considered as a second-line treatment.[7] Clinical trials evaluating the efficacy of griseofulvin in the treatment of onychomycosis have demonstrated greater clinical and/or mycological cure rates with terbinafine compared to griseofulvin.[25-28]

For the treatment of tinea capitis, guidelines recommend the use of systemic antifungals because topical agents do not penetrate the hair follicle.[5,8] Fluconazole, itraconazole, griseofulvin and terbinafine have similar efficacy and safety profiles for the treatment tinea capitis due to *Trichophyton* species.[5,8] Griseofulvin is recommended as initial therapy for the treatment of tinea capitis due to *Microsporum* species.[5] Several studies have demonstrated similar clinical cure rates with griseofulvin compared to fluconazole, itraconazole, ketoconazole and terbinafine for the treatment of cutaneous dermatophyte infections.[10,12-15,18-23,29-32] There were no studies found in the medical literature that directly compared the different formulations of griseofulvin.

There is insufficient evidence to support that one brand miscellaneous antifungal 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 miscellaneous antifungals 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 antifungal 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antituberculosis Agents
AHFS Class 081604
May 9, 2012

I. Overview

Tuberculosis is a common and often deadly infectious disease that typically affects the pulmonary system; however, all parts of the body can be affected by the disease. Tuberculosis is contracted through the inhalation of droplet nuclei containing *Mycobacterium tuberculosis* organisms, which are generated when a person with active pulmonary disease coughs, sneezes, talks or sings.[14] Following the initial infection, viable bacilli can persist for several years resulting in a latent tuberculosis infection (LTBI), which is asymptomatic and not infectious. Active disease can develop immediately after the initial exposure or after reactivation of LTBI.

The treatment of tuberculosis is a long-term process and focuses on treating active disease, as well as latent infections. Standard treatment regimens for active disease include an initial phase, which kills rapidly multiplying populations of *Mycobacterium tuberculosis*. This is followed by a continuation phase, which kills the intermittently dividing populations.[1-12] The initial phase of treatment includes ≥3 antituberculosis agents to prevent the emergence of drug resistance. Treatment of latent tuberculosis consists of monotherapy for 6-9 months. For the treatment of multi-drug resistant tuberculosis (MDR-TB), 4 second-line antituberculosis agents should be used for ≥8 months.[57]

Mycobacterium avium complex (MAC) organisms are the most common cause of nontuberculous mycobacterial disease in the U.S.[20] Rifabutin is the only antituberculosis agent approved for the prevention of disseminated MAC in patients with advanced HIV infection.

The antituberculosis agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Ethambutol, isoniazid, pyrazinamide, rifampin, and rifampin/isoniazid are available in a generic formulation. This class was last reviewed in November 2009.

Table 1. Antituberculosis Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Aminosalicylic acid	packet	Paser®	none
Capreomycin	injection	Capastat Sulfate®	none
Cycloserine	capsule	Seromycin®	none
Ethambutol	tablet	Myambutol®*	ethambutol
Ethionamide	tablet	Trecator®	none
Isoniazid	injection, syrup, tablet	N/A	isoniazid
Pyrazinamide	tablet	N/A	pyrazinamide
Rifabutin	capsule	Mycobutin®	none
Rifampin	capsule, injection	Rifadin®*	rifampin
Rifampin and isoniazid	capsule	Rifamate®*	rifampin and isoniazid
Rifampin, isoniazid, and pyrazinamide	tablet	Rifater®	none
Rifapentine	tablet	Priftin®	none

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

The antituberculosis agents 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 antituberculosis agents that are noted in Table 7. 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 anti-infective 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 Antituberculosis Agents[1-12]

Organism	Aminosalicylic Acid	Capreomycin	Cycloserine	Ethambutol	Ethionamide	Isoniazid	Pyrazinamide	Rifabutin	Rifampin	Rifapentine
Gram-Negative Aerobes										
Enterobacter species			✔							
Escherichia coli			✔					✔		
Neisseria meningitidis									✔	
Mycobacteria										
Mycobacterium avium								✔		
Mycobacterium intracellulare								✔		
Mycobacterium tuberculosis	✔	✔	✔	✔	✔	✔	✔		✔	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the antituberculosis agents are summarized in Tables 3-6.

Table 3. Treatment Guidelines Using the Antituberculosis Agents

Clinical Guideline	Recommendation(s)

Centers for Disease Control and Prevention (CDC): **Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection**[58] **(2011)**	Patients for Whom Isoniazid-Rifapentine (INH-RPT) is Recommended
	• The combination of INH and RPT given as 12 weekly directly observed therapy (DOT) doses is recommended as an equal alternative to 9 months of daily self-supervised INH for treating LTBI in otherwise healthy patients aged ≥12 years who have a predictive factor for greater likelihood of TB developing.
	• HIV-infected patients who are otherwise healthy and are not taking antiretroviral medications also are included in this category.
	• Recommendations for using the previous regimens for treating LTBI are unchanged, and the RIF-PZA regimen is not recommended.
	• The choice between INH and INH-RPT depends on feasibility of DOT, resources for drug procurement, program operations including patient monitoring, expectance of treatment completion as foreseen from medical and social circumstances of the patient, and preferences of the patient and the prescribing physician.
	• The preferred regimen for children aged 2–11 years is 9 months of daily INH.
	Patients for Whom INH-RPT is Not Recommended
	• INH-RPT is not recommended for the following patients:
	  ○ Children aged <2 years
	  ○ HIV-infected patients receiving antiretroviral treatment
	  ○ Pregnant women or women expecting to become pregnant during treatment
	  ○ Patients who have LTBI with presumed INH or RIF resistance.

World Health Organization (WHO): **Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis**[57] **(2011)**	Composition of Anti-Tuberculosis Regimens for MDR-TB • In the treatment of patients with MDR-TB, four second-line antituberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase. • In the treatment of patients with MDR-TB, a fluoroquinolone should be used. • A later-generation fluoroquinolone, rather than an earlier-generation fluoroquinolone, should be used. • In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used. • In the treatment of patients with MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (p-aminosalicylic acid) if cycloserine cannot be used. Duration of Second-Line Anti-Tuberculosis Regimens • In the treatment of patients with MDR-TB, an intensive phase of ≥8 months is recommended. • A total of ≥20 months of therapy is recommended for those without any previous MDR-TB treatment.
World Health Organization (WHO): **Treatment of Tuberculosis Guidelines**[21] **(2010)**	New Patients • New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR. • The 2HRZE/6HE treatment regimen should be phased out. • Wherever feasible, the optimal dosing frequency for new patients with

Clinical Guideline	Recommendation(s)
	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> • Specimens for culture and drug susceptibility testing (DST) should be obtained from all previously treated TB patients at or before the start of treatment. DST should be performed for at least isoniazid and rifampicin. • In settings where rapid molecular-based DST is available, the results should guide the choice of regimen. • In settings where rapid molecular-based DST results are not routinely available to guide the management of individual patients, empiric treatment should be started as follows: • TB patients whose treatment has failed1 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 treat-ment 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. • In settings where DST results are not yet routinely available to guide the management of individual patients, the empirical regimens will continue throughout the course of treatment. • NTPs should obtain and use their country-specific drug resistance data on failure, relapse and default patient groups to determine the levels of MDR. • Fixed-dose combinations (FDC) of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide) and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs are highly recommended, especially when medication ingestion is not observed. • FDCs also reduce the number of tablets to be consumed and may thereby increase patient adherence to recommended treatment regimens.

American Thoracic Society (ATS): **Hepatotoxicity of Antituberculosis Therapy[13] (2006)**	• Drug-induced liver injury (DILI) is a concern when treating patients with tuberculosis (TB).
	• DILI may occur with all currently recommended regimens for the treatment of active TB and latent TB infection (LTBI).
	<u>Treatment of LTBI</u>
	• The clinician and patient should determine the appropriate regimen together relative to the risks and the following should be considered:
	  ○ INH taken for 9 months remains the preferred regimen.
	  ○ RIF is an option for patients who may not tolerate INH, but potential drug interactions should be considered.
	  ○ Since INH with RIF is more hepatotoxic than either alone,

Clinical Guideline	Recommendation(s)
	this combination should be used with caution in patients at risk for hepatotoxicity. o For patients with alanine aminotransferase (ALT) elevations more than 2.5 to 3 times the upper limit of normal (ULN), chronic alcohol consumption, or severe liver disease (low albumin and coagulopathy or encephalopathy), the risks may outweigh the benefits; if LTBI treatment initiated, monitoring is recommended. o RIF and PZA combination is no longer recommended for the treatment of LTBI. • Interventions for hepatotoxicity include the following: o If ALT is at least three times the ULN when jaundice and/or hepatitis symptoms are reported, or if ALT is at least five times the ULN in the absence of symptoms, then INH should be withheld. An indication of more frequent monitoring would be a rapid increase in ALT. o In situations were a patient may be initiated on INH for the treatment of LTBI with baseline ALT more than three times the ULN, the treatment should be discontinued if there is more than a 2-3 fold increase in ALT above baseline. o For patients with cirrhosis, treatment with RIF and EMB, with levofloxacin, moxifloxacin, gatifloxacin, or cycloserine, for 12-18 months may be considered. • Re-challenge strategies include the following: o Once the ALT returns to less than 2 times the ULN, RIF may be started with or without EMB. o After 3-7 days, INH may be restarted while monitoring ALT. o If symptoms occur or ALT increases, the last agent added should be discontinued. <u>Treatment of TB</u> • The crucial efficacy of isoniazid and rifampin warrants their use and retention, if at all possible, even in the face of preexisting liver disease. Several regimens are recommended if baseline serum ALT is more than three times the ULN, and TB is not believed to be the cause: o Treatment without pyrazinamide might utilize isoniazid and rifampin for 9 months with ethambutol until drug susceptibility testing of the *M. tuberculosis* isolate is completed. o In patients with cirrhosis, rifampin and ethambutol, with levofloxacin, moxifloxacin, gatifloxacin, or cycloserine, for 12 to 18 months may be considered. o For patients with encephalopathic liver disease, ethambutol combined with a fluoroquinolone, cycloserine, and capreomycin or aminoglycoside for 18 to 24 months may be an option. However, these regimens have not been tested systematically. o Some providers avoid aminoglycosides in severe, unstable liver disease due to concerns about renal insufficiency, or bleeding from injected medication in patients with thrombocytopenia and/or coagulopathy. • Interventions for hepatotoxicity include: o The first-line anti-TB drugs, especially rifampin, should not be discontinued for mild gastrointestinal complaints, which may be relatively frequent in the initial weeks of anti-TB treatment. o If serum transaminase concentrations are more than five times

Clinical Guideline	Recommendation(s)
	the ULN (with or without symptoms) or more than three times the ULN with jaundice and/or hepatitis symptoms, then potentially hepatotoxic medications should be stopped immediately and the patient evaluated promptly. o Serologic tests for hepatitis A, B, and C viruses should be obtained, and the patient should be evaluated for biliary disease, use of alcohol, and other hepatotoxic drugs. o Some experts recommend interrupting treatment for lesser increases in patients with cirrhosis or encephalopathy. o If indicated, until the specific cause of abnormalities can be determined, clinicians should treat with at least three anti-TB agents that are less likely to cause hepatotoxicity. • Re-challenge strategies include the following: o After ALT returns to less than two times the ULN, rifampin may be restarted with or without ethambutol. o After 3 to 7 days, isoniazid may be reintroduced, subsequently rechecking ALT. o If symptoms recur or ALT increases, the last drug added should be stopped. o For those who have experienced prolonged or severe hepatotoxicity, but tolerate reintroduction with rifampin and isoniazid, re-challenge with pyrazinamide may be hazardous. In this circumstance, pyrazinamide may be permanently discontinued, with treatment extended to 9 months. Although pyrazinamide can be reintroduced in some milder cases of hepatotoxicity, the benefit of a shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from pyrazinamide re-challenge.
American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC)/Infectious Diseases Society of America (IDSA): **Controlling Tuberculosis in the United States[14] (2005)**	• Failure to receive and complete a standard course of treatment for tuberculosis (TB) has adverse consequences, including treatment failure, relapses, increased TB transmission, and the emergence of drug-resistant TB. • These adverse outcomes are preventable by case-management strategies provided by TB-control programs, including use of directly-observed therapy (DOT). • Patient-specific strategies for promoting adherence to treatment should take into account each patient's clinical and social circumstances and needs. • The initial strategy used should emphasize direct observation of medication ingestion by a healthcare worker. • Patient input into this process (e.g., regarding medications to be taken or the location of DOT) is often useful as it can minimize the burden of treatment and provide the patient a degree of control over an anticipated lengthy course of therapy.
Pediatric Tuberculosis Collaborative Group: **Targeted Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection in Children and Adolescents[16] (2004)**	• Treatment of latent tuberculosis infection (LTBI) with 9 months of daily isoniazid (INH) remains the recommended regimen for children and adolescents without a known source case or with a source case whose *M tuberculosi*s isolate is susceptible to INH. • Intermittent (2- or 3-times-per-week) regimens are acceptable if these regimens are administered by using a directly-observed therapy (DOT) program. • Daily rifampin (RIF) for 6 months is a suitable alternative for patients with LTBI who have been exposed to a source case whose isolate is resistant to INH but susceptible to RIF or for those who cannot tolerate INH. • Shorter-course regimens with RIF and pyrazinamide (PZA) are not

Clinical Guideline	Recommendation(s)
	recommended because of hepatotoxicity observed in adults and the lack of clinical data in children.
Centers for Disease Control and Prevention (CDC): **Adverse Event Data and Revised ATS/CDC Recommendations Against the use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection—United States[17] (2003)**	• The CDC reported data of severe liver injury in patients treated for latent tuberculosis infections (LTBI) with a daily and twice-weekly 2-month regimen of rifampin (RIF) and pyrazinamide (PZA). • It is recommended that RIF and PZA not be offered to persons with LTBI. • Clinicians are advised to use the recommended alternative regimens for the treatment of LTBI (refer to Table 6 for specific treatment regimens). • RIF and PZA should continue to be administered in multidrug regimens for the treatment of persons with active TB disease.

American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC)/Infectious Diseases Society of America (IDSA): **Treatment of Tuberculosis[15] (2003)**	• The overall goals for treatment of tuberculosis are to cure the patient and minimize the transmission of *Mycobacterium tuberculosis* to other persons.
	• There are four recommended regimens for treating patients with tuberculosis caused by drug-susceptible organisms. Each regimen has an initial phase of 2 months followed by a choice of several options for the continuation phase of either 4 or 7 months. The recommended regimens together with the number of doses specified by the regimen are described in Table 4. The initial phases are denoted by a number (1, 2, 3, or 4) and the continuation phases that relate to the initial phase are denoted by the number plus a letter designation (a, b, or c).
	• Because of the relatively high proportion of adult patients with 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. Thus, in most circumstances, the treatment regimen for all adults with previously untreated tuberculosis should consist of a 2-month initial phase of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) (Table 4, Regimens 1–3).
	• If (when) drug susceptibility test results are known and the organisms are fully susceptible, EMB need not be included.
	• 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 (Regimen 4).
	• The continuation phase (Table 4) of treatment is given for either 4 or 7 months. The 4-month continuation phase should be used in the large majority of patients. The 7-month continuation phase is recommended only for three groups:
	  ○ Patients with cavitary pulmonary tuberculosis caused by drug-susceptible organisms and whose sputum culture obtained at the time of completion of 2 months of treatment is positive
	  ○ Patients whose initial phase of treatment did not include PZA
	  ○ Patients being treated with once weekly INH and rifapentine and whose sputum culture obtained at the time of completion of the initial phase is positive
	• Refer to Table 5 for specific treatment recommendations for patients with various patterns of drug-resistant tuberculosis.
	• Although there is no evidence indicating that fixed-dose combination medications are more efficacious than administration of the individual agents, it is suggested that these formulations should be used when DOT is not possible.

American Thoracic Society	• (Recommendations were updated in 2003 – see above guideline)

Clinical Guideline	Recommendation(s)

(ATS)/Centers for Disease Control and Prevention (CDC): **Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection[18] (2000)**	• Treatment of latent tuberculosis infection (LTBI) is an essential part of the strategy to eliminate tuberculosis (TB) in the United States.
	• Persons with LTBI who are included among those at increased risk for TB should be offered treatment.
	• Four treatment regimens are recommended:
	  o Isoniazid (INH) treatment for 6 months or 9 months – HIV negative.
	  o INH should be given for 9 months –HIV positive.
	  o Rifampin (RIF) and pyrazinamide (PZA) should be given for 2 months – both HIV positive and negative.
	  o RIF should be given for 4 months for both HIV positive and HIV negative.
	• The preferred regimen for treatment of LTBI in pregnant women is INH, administered either daily or twice weekly.
	• The only recommended regimen for treatment of LTBI in HIV-uninfected children is a 9-month course of INH as self administered daily therapy or by directly observed therapy (DOT) twice weekly.
	• No studies have been published regarding the efficacy of any form of treatment for LTBI in HIV-infected children. The American Academy of Pediatrics currently recommends a 9-month course of INH.
	• The optimal length of rifampin therapy in children with LTBI is not known; however, the American Academy of Pediatrics recommends 6 months of treatment.

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[19] (2008)**	<u>Treatment of Latent Tuberculosis Infection (LTBI)</u>
	• HIV-infected persons, regardless of age, should be treated for LTBI if they have no evidence of active TB and:
	  o A positive diagnostic test for LTBI and no prior history of treatment for active or latent TB
	  o A negative diagnostic test for LTBI but are close contacts of persons with infectious pulmonary TB
	  o A history of untreated or inadequately treated healed TB (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for LTBI
	• Treatment options for LTBI include INH daily or twice weekly for 9 months.
	• Due to an increased risk of fatal and severe hepatotoxicity, a 2-month regimen of daily RIF and PZA is not recommended for LTBI treatment regardless of HIV status.
	• HIV-infected persons receiving INH should receive pyridoxine to minimize the risk of developing peripheral neuropathy. Alternatives for individuals who cannot take INH or who have been exposed to a known INH-resistant index case include either RIF or rifabutin alone for 4 months.
	• For persons exposed to INH- and/or RIF-resistant TB, decisions to treat with one or two drugs other than INH, RIF, or rifabutin should be based on the relative risk of exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities.
	• Directly observed therapy (DOT) should be used with intermittent dosing regimens when otherwise feasible to maximize regimen completion rates.
	• There is no evidence to suggest that LTBI treatment should be continued beyond the recommended duration in persons with HIV infection. Therefore, LTBI treatment should be discontinued after completing the appropriate number of doses.

Clinical Guideline	Recommendation(s)
	Treatment of Active Tuberculosis Disease • Recommendations for anti-TB treatment regimens in HIV-infected adults follow the same principles as for adults without HIV-infection. • Treatment of drug susceptible TB disease should include a 6-month regimen with an initial phase of INH, RIF or rifabutin, pyrazinamide (PZA), and ethambutol (EMB) administered for 2 months followed by INH and RIF (or rifabutin) for 4 additional months. • When drug-susceptibility testing confirms the absence of resistance to INH, RIF, and PZA, EMB may be discontinued before 2 months of treatment have been completed. • For patients with cavitary lung disease and cultures positive for *M. tuberculosis* after completion of 2 months of therapy, treatment should be extended with INH and RIF for an additional 3 months for a total of 9 months. • All HIV-infected patients treated with INH should receive pyridoxine supplementation. • For patients with extrapulmonary TB, a 6- to 9-month regimen (2 months of INH, RIF, PZA, and EMB followed by 4 to 7 months of INH and RIF) is recommended. • Exceptions to the recommendation for a 6- to 9-month regimen for extrapulmonary TB include CNS disease (tuberculoma or meningitis) and bone and joint TB, for which many experts recommend 9 to 12 months. • Adjuvant corticosteroids should be added when treating CNS and pericardial disease. • Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement. • Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over 6 to 8 weeks or prednisone 1 mg/kg for 3 weeks, then tapered for 3 to 5 weeks. *Mycobacterium avium* Complex Disease Prophylaxis • HIV-infected adults and adolescents should receive chemoprophylaxis against disseminated MAC disease if they have a CD4+ count of <50 cells/microliters. • 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 might complicate the use of this agent. • Before prophylaxis is initiated, disseminated MAC disease should be ruled out by clinical assessment, which might include obtaining a blood culture for MAC. Because treatment with rifabutin could result in RIF resistance among persons who have active TB, active TB also should be excluded before rifabutin is used for prophylaxis.

Clinical Guideline	Recommendation(s)
	Treatment of *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 clarithromycin intolerance preclude the use of clarithromycin. • EMB is the recommended second drug. Some clinicians would add rifabutin as a third drug. The addition of a third or fourth drug should be considered in persons with advanced immunosuppression (CD4+ count <50 cells/µL), high mycobacterial loads (>2 $\log_{10}$ colony forming units/mL of blood), or in the absence of effective ART, settings in which mortality is increased and emergence of drug resistance is most likely. Based on data in non-HIV-infected patients, the third or fourth drug might include an injectable agent such as amikacin or streptomycin.
American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA): **Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases[20] (2007)**	• For patients with nodular/bronchiectatic disease, a three times a week regimen consisting of clarithromycin 1,000 mg or azithromycin 500 mg, rifampin (RIF) 600 mg, and ethambutol (EMB) 25 mg/kg is recommended. The treatment regimen should be considered until the culture is negative for 1 year while on therapy. • For patients with fibrocavitary *Mycobacterium avium* complex (MAC) lung disease or severe nodular/bronchiectatic disease, a daily regimen consisting of clarithromycin 500-1,000 mg or azithromycin 250 mg, RIF 600 mg or rifabutin 150-300 mg, and EMB 15 mg/kg (with possible consideration of amikacin or streptomycin administered three times a week) is recommended. The treatment regimen should be considered until the culture is negative for 1 year while on therapy. • For patients with disseminated MAC disease, a regimen consisting of clarithromycin 1,000 mg/day or azithromycin 250 mg/day and EMB 15 mg/kg/day with or without rifabutin 150-350 mg/day is recommended. The treatment regimen can be discontinued with resolution of symptoms and reconstitution of cell-mediated immune function. • For prophylaxis of disseminated MAC disease, therapy should be initiated in adults with AIDS with CD4 T-lymphocyte counts less than 50 cells/µL and consists of azithromycin 1,200 mg/week or clarithromycin 1,000 mg/day. Rifabutin at a dose of 300 mg/day is also effective but is not tolerated as well. • For patients with *M kansasii* pulmonary disease, a regimen consisting of INH 300 mg/day, RIF 600 mg/day, EMB 15 mg/kg/day is recommended. The treatment regimen should be considered until the culture is negative for 1 year while on therapy.

DOT=directly-observed therapy, EMB=ethambutol, INH=isoniazid, LTBI=latent tuberculosis infection, MDR-TB=multiple drug-resistant tuberculosis, PZA=pyrazinamide, RIF=rifampin
H=isoniazid, R=rifampicin, Z=pyrazinamide, E=ethambutol, S=streptomycin

Table 4. ATS/CDC/IDSA-Recommended Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms[15]

Initial Phase			Continuation Phase			Range of Total Doses Minimal Duration	Rating*	
Regimen	**Drugs**	**Interval and Doses† (Minimal Duration)**	**Regimen**	**Drugs**	**Interval and Doses‡ (Minimal Duration)**		**HIV–**	**HIV+**
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 week) or 5 days/week for 40 doses (8 week)§	1a	INH/RIF	Seven days per week for 126 doses (18 week) or 5 days/week for 90 doses (18 week)	182-130 (26 week)	A(I)	A(II)
			1b	INH/RIF	Twice weekly for 36 doses (18 week)	92-76 (26 week)	A(I)	A(II)‖
			1c¶	INH/RPT	Once weekly for 18 doses (18 week)	74-58 (26 week)	B(I)	E(I)
2	INH RIF PZA EMB	Seven days per week for 14 doses (2 week), then twice weekly for 12 doses (6 week) or 5 days/week for 10 doses (2 week)§, then twice weekly for 12 doses (6 week)	2a	INH/RIF	Twice weekly for 36 doses (18 week)	62-58 (26 week)	A	B(II)‖
			2b¶	INH/RPT	Once weekly for 18 doses (18 week)	44-40	B(I)	E(I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 week)	3a	INH/RIF	Three times weekly for 54 doses (18 week)	78 (26 week)	B(I)	B(II)
4	INH RIF EMB	Seven days per week for 56 doses (8 week) or 5 days/week for 40 doses (8 week)	4a	INH/RIF	Seven days per week for 217 doses (31 week) or 5 days/week for 155 doses (31 week)	273-195 (39 week)	C(I)	C(II)
			4b	INH/RIF	Twice weekly for 62 doses (31 week)	118-102 (39 week)	C(I)	C(II)

Drug abbreviations: EMB=ethambutol; INH=isoniazid; PZA=pyrazinamide; RIF=rifampin; RPT=rifapentine

*Definitions of ratings: A=preferred; B=acceptable alternative; C=offer when A and B cannot be given; E=should never be given; I=randomized clinical trial, II=data from clinical trials that were not randomized or were conducted in other populations; III=expert opinion

†When direct observed therapy (DOT) is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicated this would be an effective practice.

‡Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

§Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimens is A.

‖Not recommended for HIV-infected patients with CD4 cell counts <100 cells/ml.

¶Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on the initial chest radiograph. For patients started on this regimen and found to have a positive culture from the two month specimen, treatment should be extended an extra three months.

Table 5. ATS/CDC/IDSA-Recommended Potential Regimens for the Management of Patients with Drug-Resistant Pulmonary Tuberculosis[15]

Pattern of Drug Resistance	Suggested Regimen	Duration of Treatment (months)
INH (±SM)	RIF, PZA, EMB (an FQN may strengthen the regimen for patients with extensive disease)	6
INH & RIF (±SM)	FQN, PZA, EMB, IA, ± alternative agent	18-24
INH, RIF (±SM), & EMB or PZA	FQN (EMB or PZA if active), IA, & 2 alternative agents	24
RIF	INH, EMB, FQN, supplemented with PZA for the first 2 months (an IA may be included for the first 2-3 months for patients with extensive disease)	12-18

EMB=ethambutol; FQN=fluoroquinolone; IA=injectable agent which may include an aminoglycoside (streptomycin, amikacin, or kanamycin) or the polypeptide capreomycin; INH=isoniazid; PZA=pyrazinamide; RIF=rifampin; SM=streptomycin; Alternative agents=ethionamide, cycloserine, aminosalicylic acid, clarithromycin, amoxicillin-clavulanate, linezolid

Table 6. ATS/CDC/IDSA-Recommended Drug Regimens for the Treatment of Latent Tuberculosis Infection (LTBI)[17]

Drug(s)	Duration (months)	Interval	Minimum # of Doses for Treatment Completion	Rating: Persons HIV-Negative*†	Rating: Persons HIV-Positive*†
Isoniazid	9	Daily	270	A (II)	A (II)
Isoniazid	9	Twice weekly	76	B (II)	B (II)
Isoniazid	6	Daily	180	B (I)	C (I)
Isoniazid	6	Twice weekly	52	B (II)	C (II)
Rifampin	4	Daily	120	B (II)	B (III)
Rifampin and pyrazinamide	2	Due to reports of severe liver injury and deaths, the combination rifampin and pyrazinamide should generally not be offered for LTBI treatment.		D (II)	D (II)

Using the US Public Health Service system, CDC and ATS have ranked these regimens according to the strength of the recommendation and the quality of supporting evidence.
*Strength of recommendation: A=preferred; B=acceptable alternative; C=offer when A and B cannot be given; D=should generally not be offered
†Quality of supporting evidence: I=randomized clinical trial data; II=data from clinical trials that are not randomized or were conducted in other populations; III=expert opinion

III. Indications

The Food and Drug Administration (FDA)-approved indications for the antituberculosis agents are noted in Tables 7-8. 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 7. FDA-Approved Indications for the Antituberculosis Agents (Drugs A-I)[1-12]

Indication	Aminosalicylic Acid	Capreomycin	Cycloserine	Ethambutol	Ethionamide	Isoniazid
Prevention of tuberculosis						✔
Treatment of active tuberculosis in patients intolerant of or refractory to isoniazid or rifampin					✔ *	
Treatment of all forms of tuberculosis						✔
Treatment of pulmonary tuberculosis	✔ *	✔ *		✔		
Treatment of pulmonary and extrapulmonary tuberculosis			✔ *			

*Second-line therapy when the primary/conventional treatments are ineffective.

Table 8. FDA-Approved Indications for the Antituberculosis Agents (Drugs P-R)[1-12]

Indication	Pyrazinamide	Rifabutin	Rifampin	Rifampin/ Isoniazid	Rifampin/ Isoniazid/ Pyrazinamide	Rifapentine
Prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection		✔				
Treatment of active tuberculosis	✔					
Treatment of all forms of tuberculosis			✔			
Treatment of pulmonary tuberculosis				✔ ^	✔ †	✔
Treatment of asymptomatic carriers of *Neisseria meningitides* to eliminate meningococci from the nasopharynx			✔			

^When the patient has been titrated on the individual components and it has been established that this fixed dosage is therapeutically effective.
†Treatment should be administered on a daily, continuous basis for 2 months only. Following this initial phase, treatment should be changed to rifampin and isoniazid.

IV. Pharmacokinetics

The pharmacokinetic parameters of the antituberculosis agents are listed in Table 9.

Table 9. Pharmacokinetic Parameters of the Antituberculosis Agents[1-12]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Aminosalicylic acid	60-65	50-60	Liver	Renal (80)	1.1-1.62
Capreomycin	Not reported	Not reported	Minimal	Renal (50-52)	4-6
Cycloserine	Not reported	Not reported	Liver (35)	Renal (50-70)	10
Ethambutol	80	10-30	Liver (10-20)	Renal (50-90) Feces (20-22)	2.5-4
Ethionamide	80	Not reported	Liver, extensive	Renal (1)	1.92
Isoniazid	90	4-30	Liver, extensive	Renal (5-30)	0.7-4
Pyrazinamide	~100	Not reported	Not reported	Renal (70)	9-23
Rifabutin	20	85	Not reported	Renal(53) Feces (30)	45
Rifampin	90-95	80	Liver (60-80) Intestinal wall (30-45)	Renal (15-30) Feces (60)	3-4
Rifampin, isoniazid, and pyrazinamide	RIF: 89 INH: 100 PZA: 97	RIF: 80 INH: minimal PZA: 10	RIF: enterohepatic INH: liver PZA: liver	RIF: Renal (up to 30) INH: Renal (50-70) PZA: Renal (70)	RIF: 3 INH: 3 PZA: 10
Rifapentine	70	98	Liver	Renal (17) Feces (70)	14-17

INH=isoniazid, PZA=pyrazinamide, RIF=rifampin

V. Drug Interactions

Significant drug interactions with the antituberculosis agents are listed in Table 10.

Table 10. Significant Drug Interactions with the Antituberculosis Agents[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Isoniazid	1	Acetaminophen	The toxic effects of acetaminophen may be increased by isoniazid.
Pyrazinamide	1	Rifamycins	The combination of rifamycins and pyrazinamide may lead to additive liver necrosis and failure as a result of hepatitis.
Rifampin	1	Dabigatran	Induction of P-glycoprotein by rifampin may decrease the absorption of dabigatran.
Rifamycins	1	Anticoagulants	The hypoprothrombinemic effect of oral anticoagulants may be decreased by rifamycins.
Rifamycins	1	Axitinib	Induction of CYP3A4 or CYP3A5 by rifamycins may increase the metabolic elimination of axitinib.
Rifamycins	1	Bortezomib	Induction of CYP3A4 by rifamycins may increase the metabolic elimination of bortezomib.
Rifamycins	1	Brentuximab	Induction of CYP3A4 by rifamycins may decrease the plasma

Generic Name(s)	Significance Level	Interaction	Mechanism
			concentrations of monomethyl auristatin E (MMAE), the microtubule disrupting agent in brentuximab.
Rifamycins	1	Crizotinib	Induction of CYP3A4 by rifamycins may increase the metabolic elimination of crizotinib.
Rifamycins	1	Cyclosporine	Rifamycins induce hepatic and intestinal metabolism (CYP3A4) of cyclosporine.
Rifamycins	1	Dienogest	Rifamycins may induce hepatic microsomal metabolism of the estrogenic and progestational components of dienogest.
Rifamycins	1	Direct factor Xa inhibitors	Induction of P-glycoprotein and CYP3A4 by rifamycins may increase the metabolic elimination of direct factor Xa inhibitors.
Rifamycins	1	HCV protease inhibitors	Induction of CYP3A4 by rifamycins may increase the metabolic elimination of HCV protease inhibitors.
Rifamycins	1	HIV protease inhibitors	Inhibition of prehepatic or hepatic cytochrome P450 3A isoenzymes by HIV protease inhibitors may increase the oral bioavailability of rifamycins. Induction of CYP3A4 by rifamycins may decrease the oral bioavailability of HIV protease inhibitors
Rifamycins	1	Imidazoles	Rifamycins induce CYP3A4-mediated metabolism of imidazoles. Conversely, imidazoles inhibit CYP3A4-mediated metabolism of rifamycins.
Rifamycins	1	Macrolide immuno-suppressants	Pharmacologic effects of macrolide immunosuppressants may be decreased by rifamycins. Immunosuppression may be inadequate.
Rifamycins	1	Oral contraceptives	Rifampin induces hepatic microsomal enzymes that result in more rapid elimination of the estrogenic and progestational components of oral contraceptives.
Rifamycins	1	Progestins	Interaction is probably due to induction of metabolism (CYP3A4) by rifamycins.
Rifamycins	1	Ranolazine	Induction of CYP3A4 by rifamycins may increase the metabolic elimination of the ranolazine.
Rifamycins	1	Rilpivirine	Induction of CYP3A4 by rifabutin Oral may increase the metabolic elimination of rilpivirine.
Rifamycins	1	Voriconazole	Rifamycins increase the metabolism (CYP3A4) of voriconazole and voriconazole inhibits the metabolism

Generic Name(s)	Significance Level	Interaction	Mechanism
			(CYP3A4) of rifabutin.
Aminosalicylic acid	2	Rifamycins	The antitubercular action of rifamycins may be decreased by aminosalicylic acid.
Capreomycin	2	Nondepolarizing neuromuscular blockers	Capreomycin enhances or prolongs neuromuscular blockade via decreased presynaptic release of acetylcholine and/or postjunctional blocking activity.
Isoniazid	2	Carbamazepine	Isoniazid is suspected to inhibit carbamazepine metabolism, and carbamazepine may increase isoniazid degradation to hepatotoxic metabolites.
Isoniazid	2	Hydantoins	Isoniazid inhibits the hepatic microsomal enzyme metabolism of hydantoins.
Isoniazid	2	Rifamycins	Rifamycins and isoniazid may cause additive adverse effects when co-administered. Hepatotoxicity may occur.
Rifampin	2	Aprepitant	Induction of cytochrome P450 3A4 isoenzymes by rifampin may increase the metabolic elimination of aprepitant.
Rifampin	2	Deferasirox	Induction of UDP-glucuronosyltransferase (UGT) by rifampin may increase the metabolic elimination of deferasirox.
Rifamycins	2	Aromatase inhibitors	Induction of cytochrome P450 3A4 isoenzymes by rifamycins may increase the metabolic elimination of aromatase inhibitors.
Rifamycins	2	Atovaquone	Plasma concentrations of atovaquone may be decreased by rifamycins.
Rifamycins	2	Benzodiazepines	The oxidative metabolism of benzodiazepines may be increased during coadministration.
Rifamycins	2	β-Blockers	The hepatic metabolism of β-blockers is increased due to enzyme induction by rifamycins.
Rifamycins	2	Bupropion	Induction of cytochrome CYP450 2B6 by rifamycins may increase the metabolic elimination of bupropion.
Rifamycins	2	Cabazitaxel	Inhibition of CYP3A4 by rifamycins may increase the metabolic elimination of cabazitaxel.
Rifamycins	2	Clopidogrel	Induction of cytochrome P450 3A4 and/or 2C19 by rifamycins may increase the metabolic transformation of clopidogrel from a prodrug to its pharmacologically active metabolite
Rifamycins	2	Corticosteroids	Induction of hepatic microsomal enzymes by rifamycins may increase the metabolic elimination of

Generic Name(s)	Significance Level	Interaction	Mechanism
			corticosteroids.
Rifamycins	2	Delavirdine	Rifamycins may increase the metabolism of delavirdine by enzyme induction (CYP3A4).
Rifamycins	2	Digitoxin	Rifamycins may increase the hepatic metabolism of digitoxin. Pharmacologic effects of digitoxin may be decreased.
Rifamycins	2	Dronedarone	Induction of CYP 3A isoenzymes by rifamycins may increase the metabolic elimination of dronedarone.
Rifamycins	2	Efavirenz	Induction of CYP P450 2B6 isoenzymes by rifamycins may reduce the blood levels of efavirenz. Induction of hepatic CYP P450 3A4, 3A5, and 3A7 isoenzymes by efavirenz may affect the blood levels of rifamycins.
Rifamycins	2	Epothilones	Induction of cytochrome CYP 3A4 isoenzymes by rifamycins may increase the metabolic elimination of epothilones.
Rifamycins	2	Erlotinib	Rifamycins may induce the metabolism (CYP3A4) of erlotinib. Erlotinib plasma concentrations may be reduced, decreasing the therapeutic effects.
Rifamycins	2	Estradiol valerate	Induction of CYP3A4 isoenzymes by rifamycins may increase the metabolic elimination of estradiol valerate.
Rifamycins	2	Eszopiclone	Induction of CYP 3A4 isoenzymes by rifamycins may increase the metabolic elimination of eszopiclone.
Rifamycins	2	Fluconazole	Rifamycins may increase the metabolism of fluconazole by inducing hepatic microsomal enzymes. Fluconazole may also inhibit cytochrome P450 3A4.
Rifamycins	2	Gefitinib	Rifamycins may increase the metabolism (CYP3A4) of gefitinib during coadministration.
Rifamycins	2	Haloperidol	Induction of haloperidol metabolism by rifamycins is suspected.
Rifamycins	2	Hydantoins	Rifampin increases the hepatic microsomal enzyme metabolism of hydantoins.
Rifamycins	2	Ivacaftor	Induction of CYP3A by rifamycins may increase the metabolic elimination of ivacaftor.
Rifamycins	2	Integrase inhibitors	Induction of uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) by rifamycins may increase the metabolic elimination of

Generic Name(s)	Significance Level	Interaction	Mechanism
			integrase inhibitors.
Rifamycins	2	Imatinib	Interaction is due to increased metabolism (CYP3A4) of imatinib by rifamycins.
Rifamycins	2	Indinavir	Indinavir may decrease rifamycin metabolism (CYP3A4), while rifamycin may increase the metabolism of indinavir.
Rifamycins	2	Ivacaftor	Induction of CYP3A by rifamycins may increase the metabolic elimination of ivacaftor.
Rifamycins	2	Lamotrigine	Interaction is due to induction of hepatic enzymes responsible for the glucuronidation of lamotrigine.
Rifamycins	2	Lurasidone	Induction of CYP3A4 by rifabutin may increase the metabolic elimination of lurasidone.
Rifamycins	2	Macrolides and ketolides	Pharmacologic and toxic effects of rifamycins may be increased by macrolides and ketolides. Plasma concentrations and pharmacologic effects of macrolides and ketolides may be decreased by rifamycins.
Rifamycins	2	Maraviroc	The pharmacologic effects of maraviroc may be decreased by rifamycins.
Rifamycins	2	Meglitinides	Rifamycins may increase metabolism (CYP3A4) of the meglitinides during the first-pass and elimination phases.
Rifamycins	2	Melatonin receptor agonists	Plasma concentrations and pharmacologic effects of melatonin receptor agonists may be decreased be rifamycins. Reductions in efficacy of melatonin receptor agonists may be expected.
Rifamycins	2	Methadone	Pharmacologic effects of methadone may be decreased by rifamycins. Methadone withdrawal may be precipitated.
Rifamycins	2	Mexiletine	The antiarrhythmic action of mexiletine may be decreased by rifamycins.
Rifamycins	2	MTOR inhibitors	Pharmacologic effects of MTOR inhibitors may be decreased by rifamycins.
Rifamycins	2	Mycophenolate	Plasma concentrations and pharmacologic effects of mycophenolate may be decreased by concomitant administration of rifamycins.
Rifamycins	2	Narcotic analgesics	Rifamycins may decrease pharmacologic effects and plasma concentrations of narcotic analgesics. Pain control may be decreased.
Rifamycins	2	Nevirapine	Reduced nevirapine concentrations are listed in the manufacturer's

Generic Name(s)	Significance Level	Interaction	Mechanism
			package labeling as a possibility when rifamycins and nevirapine are coadministered.
Rifamycins	2	Nifedipine and derivatives	Rifamycins may induce hepatic enzymes and increase the first-pass metabolism of nifedipine and derivatives.
Rifamycins	2	NNRT inhibitors	Plasma concentrations and pharmacologic effects of NNRT inhibitors may be decreased by rifamycins.
Rifamycins	2	Praziquantel	Induction of cytochrome P450 3A4 isoenzymes by rifamycins may increase the metabolic elimination of praziquantel.
Rifamycins	2	Propafenone	Rifamycins may induce the hepatic microsomal enzymes responsible for metabolizing propafenone.
Rifamycins	2	Quetiapine	Plasma concentrations and pharmacologic effects of quetiapine may be decreased when co-administered with rifamycins. Reductions in therapeutic effect may occur.
Rifamycins	2	Quinidine	Increased metabolism of quinidine due to induction of hepatic microsomal enzymes by rifamycins.
Rifamycins	2	Quinine derivatives	Rifamycins increase the hepatic metabolism of quinine derivatives during coadministration.
Rifamycins	2	Ranolazine	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by rifamycins.
Rifamycins	2	Roflumilast	Induction of CYP3A4 by rifamycins may increase the metabolic elimination of roflumilast and roflumilast N-oxide, the active metabolite of roflumilast.
Rifamycins	2	Statins	Pharmacologic effects and plasma concentrations of statins may be decreased by rifamycins. Impaired cholesterol-lowering efficacy of statins may result.
Rifamycins	2	Sulfones	Plasma concentrations and pharmacologic effects of sulfones may be decreased by rifamycins. The antimicrobial effectiveness of sulfones may be reduced.
Rifamycins	2	Sulfonylureas	The pharmacologic effects of sulfonylureas may be decreased by rifamycins.
Rifamycins	2	Thiazolidinediones	Hepatic metabolism of thiazolidinediones (CYP2C8) may be increased by rifamycins.
Rifamycins	2	Ticagrelor	Induction of CYP3A4 by rifamycins may increase the metabolic

Generic Name(s)	Significance Level	Interaction	Mechanism
			elimination of ticagrelor and its active metabolite.
Rifamycins	2	Tocainide	The antiarrhythmic effectiveness of tocainide may be decreased by rifamycins.
Rifamycins	2	Tolvaptan	Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by rifamycins compromising therapeutic effectiveness.
Rifamycins	2	Tyrosine kinase receptor inhibitors	Plasma concentrations and pharmacologic effects of tyrosine kinase receptor inhibitors may be decreased by rifamycins. A reduction in therapeutic effectiveness of tyrosine kinase receptor inhibitors may occur.
Rifamycins	2	Ulipristal	Induction of CYP3A4 enzymes by rifamycins may increase the metabolic elimination of ulipristal.
Rifamycins	2	Vandetanib	Induction of CYP3A4 by rifamycins may increase the metabolic elimination of vandetanib.
Rifamycins	2	Verapamil and derivatives	Plasma concentrations and pharmacologic effects of verapamil and derivatives may be decreased by rifamycins.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the antituberculosis agents are listed in Table 11. The boxed warnings for the antituberculosis agents are listed in Tables 12-13.

Table 11. Adverse Drug Events (%) Reported with the Antituberculosis Agents[1-12]

Adverse Events	Aminosalicylic Acid	Capreomycin	Cycloserine	Ethambutol	Ethionamide	Isoniazid	Pyrazinamide	Rifabutin	Rifampin	Rifapentine
Cardiovascular										
Chest pain	-	-	-	-	-	-	-	1	-	6
Congestive heart failure	-	-	✔	✔	-	-	-	-	-	-
Hypertension	-	-	-	-	-	-	-	-	-	2
Myocarditis	-	-	-	✔	-	-	-	-	-	-
Pericarditis	✔	-	-	-	-	-	-	-	-	-
Postural hypotension	-	-	-	-	✔	-	-	-	-	-
Central Nervous System										
Aggression	-	-	✔	-	-	-	-	-	-	✔
Ataxia	-	-	-	-	-	-	-	-	✔	-
Coma	-	-	✔	-	-	-	-	-	-	-
Confusion	-	-	✔	✔	-	✔	-	-	✔	-
Drowsiness	-	-	✔	-	✔	-	-	-	✔	-
Encephalopathy	✔	-	-	-	-	✔	-	-	-	-
Fatigue	-	-	-	-	-	✔	-	-	✔	1
Fever	✔	✔	-	✔	-	✔	✔	2	✔	1
Hallucinations	-	-	-	✔	-	-	-	-	-	-
Headache	-	-	✔	✔	✔	-	-	3	✔	4
Hyperirritability	-	-	✔	-	-	-	-	-	-	-
Hyperreflexia	-	-	✔	-	-	-	-	-	-	-
Insomnia	-	-	-	-	-	-	-	1	-	1
Malaise	-	-	-	✔	-	✔	-	-	-	-
Numbness	-	-	-	-	-	-	-	-	✔	-
Paresthesia	-	-	✔	✔	-	✔	-	-	-	-
Peripheral neuropathy	-	-	-	-	-	✔	-	-	-	-
Psychosis	-	-	✔	-	✔	✔	-	-	✔	-
Restlessness	-	-	-	-	✔	-	-	-	-	-
Seizures	-	-	✔	-	-	✔	-	-	-	-
Tremor	-	-	✔	-	-	-	-	-	-	1
Vertigo	-	✔	✔	✔	✔	-	-	-	-	<1
Dermatologic										

Adverse Events	Aminosalicylic Acid	Capreomycin	Cycloserine	Ethambutol	Ethionamide	Isoniazid	Pyrazinamide	Rifabutin	Rifampin	Rifapentine
Acne	-	-	-	-	✔	-	✔	-	-	3
Maculopapular rash	-	✔	-	-	-	✔	-	-	-	2
Photosensitivity	-	-	-	-	✔	-	✔	-	-	-
Pruritus	-	-	-	✔	-	-	✔	-	✔	4
Rash	✔	✔	✔	✔	✔	✔	✔	11	✔	6
Skin discoloration	-	-	-	-	-	-	-	<1	-	✔
Urticaria	-	✔	-	-	-	-	✔	-	✔	-
Endocrine and Metabolic										
Goiter	✔	-	-	-	-	-	-	-	-	-
Gout	-	-	-	-	-	-	-	-	-	1
Gynecomastia	-	-	-	-	-	✔	-	-	-	-
Pellagra	-	-	-	-	✔	✔	-	-	-	-
Gastrointestinal										
Abdominal pain	✔	-	-	✔	✔	-	-	4	-	2
Anorexia	-	-	-	✔	✔	✔	✔	2	✔	6
Constipation	-	-	-	-	-	-	-	-	-	<1
Diarrhea	✔	-	-	-	✔	✔	-	3	✔	<1
Dyspepsia	-	-	-	-	-	-	-	3	-	3
Epigastric distress	-	-	-	-	-	✔	-	-	✔	-
Eructation	-	-	-	-	-	-	-	3	-	-
Esophagitis	-	-	-	-	-	-	-	-	-	✔
Excessive salivation	-	-	-	-	✔	-	-	-	-	-
Flatulence	-	-	-	-	-	-	-	2	✔	-
Gastritis	-	-	-	-	-	-	-	-	-	✔
Gastrointestinal upset	-	-	-	✔	-	-	-	-	-	-
Heartburn	-	-	-	-	-	-	-	-	✔	-
Nausea	✔	-	-	✔	✔	✔	✔	6	✔	3
Pancreatitis	-	-	-	-	-	-	-	-	-	✔
Pseudomembranous colitis	-	-	-	-	-	-	-	-	1-2	-
Stomatitis	-	-	-	-	✔	-	-	-	-	-
Taste perversions	-	-	-	-	✔	-	-	3	-	-
Vomiting	✔	-	-	✔	✔	✔	✔	1	✔	3
Weight loss	-	-	-	-	✔	-	-	-	-	-
Genitourinary										
Discolored urine	-	-	-	-	-	-	-	30	-	-
Dysuria	-	-	-	-	-	-	✔	-	-	-

Adverse Events	Aminosalicylic Acid	Capreomycin	Cycloserine	Ethambutol	Ethionamide	Isoniazid	Pyrazinamide	Rifabutin	Rifampin	Rifapentine
Urinary casts	-	-	-	-	-	-	-	-	-	8
Hematologic										
Agranulocytosis	✔	-	-	-	-	✔	-	-	✔	-
Anemia	✔	-	-	-	-	✔	-	6	✔	12
Eosinophilia	-	>5	-	✔	-	✔	-	1	✔	-
Hematoma	-	-	-	-	-	-	-	-	-	✔
Hemolysis	-	-	-	-	-	-	-	<1	✔	-
Leukocytosis	-	✔	-	-	-	-	-	-	-	3
Leukopenia	✔	✔	-	✔	-	-	-	17	✔	7
Lymphopenia	-	-	-	-	-	-	-	-	-	13
Neutropenia	-	-	-	✔	-	-	-	25	-	13
Neutrophilia	-	-	-	-	-	-	-	-	-	3
Thrombocytopenia	✔	✔	-	✔	✔	✔	✔	5	✔	3
Thrombocytosis	-	-	-	-	-	-	-	-	-	6
Hepatic										
Abnormal LFTs	-	✔	✔	✔	✔	✔	-	✔	✔	✔
Bilirubinemia	-	-	-	-	-	✔	-	-	-	✔
Hepatitis	✔	-	-	-	✔	✔	✔	<1	✔	✔
Jaundice	✔	-	-	-	✔	✔	-	-	✔	-
Laboratory Test Abnormalities										
BUN increased	-	36	-	-	-	-	-	-	✔	-
Hyperglycemia	-	-	-	-	-	✔	-	-	-	4
Hyperkalemia	-	-	-	-	-	-	-	-	-	✔
Hyperuricemia	-	-	-	-	-	-	-	-	-	32
Hypocalcemia	-	✔	-	-	-	-	-	-	-	-
Hypoglycemia	✔	-	-	-	-	-	-	-	-	10
Hypokalemia	-	✔	-	-	-	-	-	-	-	9
Hypomagnesemia	-	✔	-	-	-	-	-	-	-	-
Serum creatinine increased	-	✔	-	-	-	-	-	-	-	-
Uric acid increased	-	-	-	✔	-	-	-	-	✔	-
Musculoskeletal										
Arthralgia	-	-	-	-	-	-	-	<1	-	4
Dysarthria	-	-	✔	-	-	-	✔	-	-	-
Myalgia	-	-	-	-	-	-	✔	2	✔	-
Myositis	-	-	-	-	-	-	-	<1	-	-
Renal										

Adverse Events	Aminosalicylic Acid	Capreomycin	Cycloserine	Ethambutol	Ethionamide	Isoniazid	Pyrazinamide	Rifabutin	Rifampin	Rifapentine
Acute renal failure	-	-	-	-	-	-	-	-	✔	-
Acute tubular necrosis	-	✔	-	-	-	-	-	-	✔	-
Hematuria	-	-	-	-	-	-	-	-	✔	18
Hemoglobinuria	-	-	-	-	-	-	-	-	✔	-
Interstitial nephritis	-	-	-	-	-	-	✔	-	✔	-
Nephrotoxicity	-	✔	-	-	-	-	-	-	-	-
Proteinuria	-	-	-	-	-	-	-	-	-	13
Pyuria	-	-	-	-	-	-	-	-	-	22
Special Senses										
Clinical hearing loss	-	3	-	-	-	-	-	-	-	-
Color blindness	-	-	-	✔	-	-	-	-	-	-
Conjunctivitis	-	-	-	-	-	-	-	-	✔	3
Optic neuritis	✔	-	-	✔	✔	✔	-	-	-	-
Subclinical hearing loss	-	11	-	-	-	-	-	-	-	-
Tinnitus	-	✔	-	-	-	-	-	-	-	-
Visual acuity decreases	-	-	-	✔	-	-	-	-	-	-
Visual changes	-	-	-	-	-	-	-	-	✔	-
Visual defect	-	-	-	✔	-	-	-	-	-	-
Other										
Anaphylactic reactions	-	-	-	✔	-	-	-	-	✔	-
Bleeding at injection site	-	✔	-	-	-	-	-	-	-	-
Edema	-	-	-	-	-	-	-	-	✔	1
Flushing	-	-	-	-	-	-	-	-	✔	-
Hypersensitivity	-	-	-	✔	-	✔	✔	-	-	-
Joint pain	-	-	-	✔	-	-	-	-	-	-
Pain	-	-	-	-	-	-	-	1	-	6
Pain at injection site	-	✔	-	-	-	-	-	-	-	-
Pulmonary infiltrates	✔	-	-	✔	-	-	-	-	-	-
Rheumatic syndrome	-	-	-	-	-	✔	-	-	-	-
Sterile abscesses	-	✔	-	-	-	-	-	-	-	-
SLE-like syndrome	-	-	-	-	-	✔	-	-	-	-
Vasculitis	✔	-	-	-	-	-	-	-	-	-
Weakness	-	-	-	-	-	✔	-	-	✔	-

✔ Percent not specified
- Event not reported

Table 12. Boxed Warning for Capreomycin[1]

WARNING
The use of capreomycin for injection, USP in patients with renal insufficiency or preexisting auditory impairment must be undertaken with great caution, and the risk of additional cranial nerve VIII impairment or renal injury should be weighed against the benefits derived from therapy. Since other parenteral antituberculosis agents (streptomycin, viomycin) also have similar and sometimes irreversible toxic effect, particularly on cranial nerve VIII and renal function, simultaneous administration of these agents with capreomycin is not recommended. Use with non-antituberculosis drugs (polymyxin A sulfate, colistin sulfate, amikacin, gentamicin, tobramycin, vancomycin, kanamycin, and neomycin) having ototoxic or nephrotoxic potential should be undertaken only with great caution. Pregnancy: The safety of the use capreomycin in pregnancy has not been determined. Children: Safety and effectiveness in pediatric patients have not been established.

Table 13. Boxed Warning for Isoniazid[1]

WARNING
Hepatitis: Severe and sometimes fatal hepatitis associated with isoniazid therapy has been reported and may occur or may develop even after many months of treatment. The risk of developing hepatitis is age related. Approximate case rates by age are as follows: less than 1/1,000 for persons younger than 20 years of age, 3/1,000 for persons in the 20- to 34-years of age group, 12/1,000 for persons in the 35- to 49-years of age group, 23/1,000 for persons in the 50- to 64-years of age group, and 8/1,000 for persons older than 65 years of age. The risk of hepatitis is increased with daily consumption of alcohol. Precise data to provide a fatality rate for isoniazid-related hepatitis is not available; however, in a US public health service surveillance study of 13,838 persons taking isoniazid, there were 8 deaths among 174 cases of hepatitis. Therefore, carefully monitor patients given isoniazid and interview patients at monthly intervals. For persons older than 35 years of age, in addition to monthly symptom reviews, measure hepatic enzymes (specifically, AST and ALT) prior to starting isoniazid therapy and periodically throughout treatment. Isoniazid-associated hepatitis usually occurs during the first 3 months of treatment. Usually, enzyme levels return to normal despite continuance of drug, but, in some cases, progressive liver dysfunction occurs. Other factors associated with an increased risk of hepatitis include daily use of alcohol, chronic liver disease, and injection drug use. A recent report suggests an increased risk of fatal hepatitis associated with isoniazid among women, particularly black and Hispanic women. The risk may also be increased during the postpartum period. Consider more careful monitoring in these groups, possibly including more frequent laboratory monitoring. If abnormalities of liver function exceed 3 to 5 times the upper limit of normal (ULN), strongly consider discontinuation of isoniazid. Liver function tests are not a substitute for a clinical evaluation at monthly intervals or for the prompt assessment of signs or symptoms of adverse reactions occurring between regularly scheduled evaluations. Instruct patients to immediately report signs or symptoms consistent with liver damage or other adverse reactions. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of the hands and feet, persistent fatigue, weakness or fever of greater than 3-day duration or abdominal tenderness, especially right-upper-quadrant discomfort. If these symptoms appear or if signs suggestive of hepatic damage are detected, promptly discontinue isoniazid, because continued use of the drug in these cases has been reported to cause a more severe form of liver damage. Give patients with tuberculosis who have hepatitis attributed to isoniazid appropriate treatment with alternative drugs. If isoniazid must be reinstituted, do so only after symptoms and laboratory abnormalities have cleared. Restart the drug in very small and gradually increasing doses and withdraw immediately if there is any indication of recurrent liver involvement. Treatment should be deferred in persons with acute hepatic diseases.

VII. Dosing and Administration

The usual dosing regimens for the antituberculosis agents are listed in Table 14.

Table 14. Usual Dosing Regimens for the Antituberculosis Agents[1-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Aminosalicylic acid	Tuberculosis: 4 g three times per day	Tuberculosis: Correspondingly smaller doses in children than adults	Packet: 4 g
Capreomycin	Tuberculosis: Initial: 1 g daily for 60 to 120 days Maintenance: 1 g two or three times weekly for 12-24 months; maximum 20 mg/kg/day	Safety and efficacy in children have not been established.	Injection: 1 g
Cycloserine	Tuberculosis: 250 mg twice daily every 12 hours for the first 2 weeks. The usual dose is 500 mg to 1g daily	Safety and efficacy in children have not been established.	Capsule: 250 mg
Ethambutol	Tuberculosis: Initial: 15 mg/kg once daily Retreatment: 25 mg/kg once daily for 60 days; maintenance 15 mg/kg once daily	Tuberculosis: ≥13 years of age: Initial: 15 mg/kg once daily Retreatment: 25 mg/kg once daily for 60 days; maintenance 15 mg/kg once daily	Tablet: 100 mg 400 mg
Ethionamide	Tuberculosis: Initial, 250 mg/day for 1-2 days, then increase to 250 mg twice daily for 1-2 days, with gradual increases to highest tolerated dose; maximum dose 1 g/day	Tuberculosis: 10 to 20 mg/kg daily in 2 or 3 divided doses or 15 mg/kg as a single daily dose	Tablet: 250 mg
Isoniazid	Tuberculosis: Prevention: 300 mg daily for 9 months Treatment: 5 mg/kg once daily (maximum 300 mg/dose) or 15 mg/kg 1 to 3 times per week (maximum 900 mg/dose)	Tuberculosis: Prevention: 10 mg/kg daily for 6-12 months (maximum 300 mg/dose) Treatment: 10 to 15 mg/kg daily (maximum 300 mg/dose) or 20 to 40 mg/kg twice per week (maximum 900 mg/dose)	Injection: 100 mg/ml Syrup: 50 mg/5 ml Tablet: 100 mg 300 mg
Pyrazinamide	Tuberculosis: 15 to 30 mg/kg once daily (maximum 3 g/day) or 50-75 mg/kg twice weekly based on lean body weight	Tuberculosis: 15 to 30 mg/kg once daily (maximum 3 g/day) or 50-75 mg/kg twice weekly based on lean body weight	Tablet: 500 mg
Rifabutin	Prevention of Disseminated *Mycobacterium avium* Complex (MAC) Disease: 300 mg once daily or 150 mg 2 times daily	Safety and efficacy in children have not been established.	Capsule: 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Rifampin	Asymptomatic Carriers of *Neisseria meningitides* to Eliminate *meningococci* from the Nasopharynx: 600 mg twice daily for 2 days Tuberculosis: 10 mg/kg once daily; maximum 600 mg/day	Asymptomatic Carriers of *Neisseria meningitides* to Eliminate *meningococci* from the Nasopharynx: <1 month of age: 5 mg/kg every 12 hours for 2 days ≥1 month of age: 10 mg/kg every 12 hours for 2 days; maximum 600 mg per dose Tuberculosis: 10-20 mg/kg once daily; maximum 600 mg/day	Capsule: 150 mg 300 mg Injection: 600 mg
Rifampin and isoniazid	Tuberculosis: 2 capsules (600 mg rifampin, 300 mg isoniazid) once daily	Safety and efficacy in children have not been established.	Capsule: 300-150 mg
Rifampin, isoniazid, and pyrazinamide	Tuberculosis: <44 kg: 4 tablets daily 45-54 kg: 5 tablets daily ≥55kg: 6 tablets daily	Safety and efficacy in children <15 years of age have not been established.	Tablet: 120-50-300 mg
Rifapentine	Tuberculosis: Initial: 600 mg twice a week for 2 months Continuation: 600 mg once weekly for 4 months	Tuberculosis: ≥12 years of age: Initial: 600 mg twice a week for 2 months Continuation: 600 mg once weekly for 4 months	Tablet: 150 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antituberculosis agents are summarized in Table 15.

Table 15. Comparative Clinical Trials with the Antituberculosis Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treatment of Tuberculosis Infection in HIV-Negative Patients				
Conde et al.[47] (2009) Ethambutol 15-20 mg/kg, plus isoniazid 300 mg, rifampicin 450 mg (<50 kg) or 600 mg (>50 kg), and pyrazinamide 20–25 mg/kg by directly-observed therapy for 8 weeks vs moxifloxacin 400 mg plus isoniazid 300 mg, rifampicin 450 mg (<50 kg) or 600 mg (>50 kg), and pyrazinamide 20–25 mg/kg by directly-observed therapy for 8 weeks At the end of 8 weeks, all patients	RCT, DB Patients ≥18 years of age with clinical signs and symptoms of pulmonary tuberculosis, including an abnormal chest radiograph and at least one sputum smear with acid-fast bacilli	N=146 Up to 18 months	Primary: Proportion of patients with negative sputum cultures after 8 weeks of treatment Secondary: Adverse events, mortality, treatment discontinuation, tuberculosis reoccurrence	Primary: Patients assigned to moxifloxacin became culture negative more rapidly than those assigned to ethambutol. After week 1, 13% of patients in the moxifloxacin group had negative sputum cultures compared with 3% of patients in the ethambutol group (P=0.03). At every week after enrollment, patients assigned to moxifloxacin had a higher rate of culture conversion than those assigned to ethambutol (difference was significant at all time points apart from weeks 6 and 7). The median time to consistently negative cultures was 35 days for patients in the moxifloxacin group compared with 48.5 days for patients receiving ethambutol (P=0.005). Treatment with ethambutol was associated with a smaller proportion of patients with negative sputum cultures after 8 weeks of treatment (73.8%) compared to moxifloxacin (92.2%) in the univariate and multivariate analyses (OR 1.86; P=0.0001 and OR 1.75; P=0.0009, respectively). Secondary: Adverse events did not differ by treatment group. There were 16 serious adverse events (eight in each group) in 12 patients; one grade 3 cutaneous reaction in the ethambutol group was judged to be related to study drugs by the treating physicians who were not aware of treatment assignment. All other serious adverse events were judged not related to study drugs. Eight patients died during the study, including one in each group still receiving study phase treatment. No death was attributed to study treatment. Only five patients discontinued treatment because of toxic effects; two patients in the moxifloxacin group stopped because of grade 2 nausea and vomiting and one because of grade 2 paraesthesia and ataxia. Two patients in the ethambutol group stopped because of grade 2 rash and pruritus and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
were placed on open-label treatment with isoniazid and rifampicin two times per week to complete another 4 months of treatment.				one because of grade 3 peripheral neuropathy. No clinically or statistically significant changes in the QTc interval were recorded in patients in either group of the trial. Seven patients (5%) had recurrence of tuberculosis confirmed by positive culture and compatible clinical symptoms: three patients in the moxifloxacin group (at 11, 16, and 27 months after completing treatment) and four in the ethambutol group (at 6, 7, 22, and 32 months after completion). Six of seven isolates were tested for drug resistance, and all remained susceptible to isoniazid and rifampicin.
Hong Kong Chest Service et al.[30] (1987) Isoniazid, rifampin, pyrazinamide, streptomycin and ethambutol given 3 times a week vs isoniazid, rifampin, pyrazinamide, streptomycin but no ethambutol given 3 times a week vs isoniazid, rifampin, pyrazinamide, ethambutol but no	RCT Patients with sputum-smear-positive pulmonary tuberculosis	N=833 5 year	Primary: Rate of bacteriologic response and bacteriologic relapse in pts with drug-susceptible strains at 2 years Secondary: Rate of relapse at 5 years	Primary: For patients with drug-susceptible strains; bacteriologic relapse during the 2 years occurred in 1.4% of patients treated with pyrazinamide regimens compared with 7.8% of patients treated with a non-pyrazinamide regimen (P<0.001). Secondary: The total relapse rates for patients with drug-susceptible strains were 3.4% for the pyrazinamide regimens compared with 10.3% for the non-pyrazinamide regimens (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
streptomycin given 3 times a week vs isoniazid, rifampin, pyrazinamide, ethambutol given every day vs isoniazid, rifampin, streptomycin, and ethambutol given 3 times a week				
Su et al.[41] (2002) Isoniazid, rifampin, ethambutol and pyrazinamide in a fixed-dose combination (FDC) formulation^ for 2 months, followed by isoniazid and rifampin (FDC) for 4 months vs isoniazid,	RCT Patients with newly diagnosed smear-positive pulmonary tuberculosis	N=105 2 years	Primary: Development of resistance, sputum conversion, compliance and radiological improvement Secondary: Safety	Primary: A total of 51 patients were available for evaluation after 2 years. Four patients in the FDC group (7.0%) had bacilli resistant to pyrazinamide. Two patients (4.2%) had bacilli resistant to ethambutol and 6 patients (12.5%) had bacilli resistant to pyrazinamide in the group that received separate formulations. The two regimens were of similar effectiveness with regard to sputum conversion, compliance and radiological improvement. Secondary: No patient with FDC treatment developed gastrointestinal symptoms, visual disturbance or peripheral neuropathy (P<0.05). FDC treatment resulted in drug-induced fever in one patient. One patient in the FDC group relapsed 5 months after completing treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rifampin, ethambutol and pyrazinamide taken as separate tablets for 2 months, then isoniazid and rifampin taken as separate tablets for 4 months				
Teo et al.[42] (1999) Isoniazid, rifampin, and pyrazinamide fixed-dose combination (FDC) formulation once daily for 6 months, followed by intermittent treatment with isoniazid and rifampin given 3 times per week vs isoniazid, rifampin, and pyrazinamide administered as separate formulations, followed by intermittent	RCT, OL Patients with pulmonary tuberculosis	N=310 5 years	Primary: Relapse rates Secondary: Adverse events	Primary: At the end of 5 years, there were 15 relapses: 3 (2.2%) in the separate drugs group and 12 (9.3%) in the FDC group. Exclusion of 2 cases in the FDC group, one with silicotuberculosis and another with no bacteriological confirmation of diagnosis, gave a relapse rate of 7.9% (P=0.03 for the comparison of relapse rates in the 2 groups). Secondary: The frequency of adverse events was similar in both groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treatment with isoniazid and rifampin given 3 times per week				
Macnab et al.[43] (1994) Isoniazid, rifampin, and pyrazinamide fixed-dose combination (FDC) formulation vs isoniazid, rifampicin, pyrazinamide and ethambutol administered as separate formulations	RCT Adults with a first episode of pulmonary tuberculosis	N=106 Duration not specified	Primary: Rate of conversion to a negative sputum culture Secondary: Rate of inadequate compliance and side effects	Primary: All patients who took the treatment as prescribed (67 patients receiving the FDC formulation and 30 patients receiving the 4-drug regimen as separate formulations) converted to a negative sputum culture by the time 90 doses had been taken. Secondary: The rates of inadequate compliance and of side effects were similar in the two groups.
Lienhardt et al.[53] (2011) Rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, ethambutol 275 mg in a fixed-dose combination (FDC) once daily for 8 weeks vs	OL, MC, RCT Adults with newly diagnosed pulmonary tuberculosis who have received less than 4 weeks of antibiotic therapy	N=1,585 30 months	Primary: Negative culture at 18 months post randomization Secondary: Safety	Primary: The per-protocol analysis shows that 18 months after the start of treatment, 93.9% of patients in the FDC group had a favorable outcome vs 94.6% in the control group (90% CI, −3.0% to 1.5%). This was within the predefined margin of non-inferiority. In the modified ITT analysis, 83.3% of patients in the FDC group had a favorable outcome compared with 84.8% of patients in the control group (90% CI, −4.7% to 1.8%). Secondary: A total of 67 patients (31 in the FDC group and 36 in the control group) reported at least 1 adverse event. They were primarily dermatologic, rheumatologic, hepatic, or gastrointestinal disorders and were mostly of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, ethambutol 275 mg in separate formulations once daily for 8 weeks Both groups: continuation therapy with rifampicin 150 mg and isoniazid 150 mg three times weekly for 18 weeks (control)				mild or moderate severity. They were similarly distributed among the treatment groups (P=0.10).
Hong Kong Chest Service[45] (1991) Isoniazid and rifampin for 6 months, streptomycin for the first 4 months and pyrazinamide for the first 2 months (Group Z2) vs isoniazid and rifampin for 6 months, streptomycin for	RCT Patients with sputum smear-positive pulmonary tuberculosis	N=1,386 3 years (6 months of active treatment and 30 months of follow-up)	Primary: Bacteriologic failure and relapse rates	Primary: Bacteriologic failure occurred in 4 patients, all in the Z6noS group (2%; P<0.005 for the comparison with the SM-containing regimens). During 30 months of follow-up after the end of chemotherapy, bacteriologic relapse occurred in 3% of patients in the Z2 group receiving the FDC product and in 3% of patients in the Z2 group who received treatment with separate formulations. Relapse occurred in 3% of patients in the Z4 group who received the FDC product and in 6% of patients in the Z4 group who received treatment with separate formulations. Relapse occurred in 6% of patients in the Z6 group receiving the FDC product and in 1% of patients in the Z6 group who received treatment with separate formulations. Relapse occurred in 9% of patients in the Z6noS group receiving the FDC product and in 4% of patients in the Z6noS group who received treatment with separate formulations.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
the first 4 months and pyrazinamide for the first 4 months (Group Z4) vs Isoniazid and rifampin for 6 months, streptomycin for the first 4 months and pyrazinamide for the first 6 months (Group Z6) vs isoniazid and rifampin for 6 months, and pyrazinamide for 6 months (Group Z6noS) During the later part of the study, patients were allocated at random to receive isoniazid, rifampin, and pyrazinamide either as a fixed-dose combination				There were no significant differences in relapse rates with the FDC regimens and the separate-drug regimens. There were no significant differences in relapse rates among the regimens with different durations of pyrazinamide, or among the regimens with and without streptomycin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(FDC) or as three separate formulations.				
Cowie et al.[46] (1990) Isoniazid, rifampin and pyrazinamide administered as a fixed-dose combination (FDC) 5 tablets per day on weekdays for 100 treatment days (RHZ) vs streptomycin, isoniazid, rifampin and pyrazinamide administered as separate formulations (RHZS)	RCT Male gold miners with a first case of tuberculosis	N=150 100 treatment days	Primary: Treatment success Secondary: Rates of non-compliance	Primary: Treatment was unsuccessful in 10 patients in the RHZ group, 4 men were lost to follow-up, 3 cases of failure of conversion of sputum on the regimen, and 3 relapses. The results for the separate-drug group were similar, with 4 lost to follow-up, 2 treatment failures and 4 relapses. Secondary: Noncompliance was detected in 42% of the RHZ group and in 16% of the RHZS group.
Gonzalez-Montaner et al.[25] (1994) Rifampin (rifampicin*) 150 mg daily for 6 months vs rifabutin 150 mg	MC, RCT HIV-negative patients with newly-diagnosed drug-sensitive, radio-graphically active and bacteriologically confirmed pulmonary tuberculosis	N=520 2 years	Primary: Bacteriologic conversion rates, median time to culture conversion Secondary: Signs and symptoms of tuberculosis	Primary: Considering all patients with positive baseline culture, the success rates for each patient were 89%, 94% and 92% in the rifampin 150 mg, rifabutin 150 mg, and rifabutin 300 mg groups, respectively (P=0.357). The median time to culture conversion was comparable in the 3 groups and was 34 days for rifampin and 37 days for each of the rifabutin groups. Secondary: There was no significant difference between the treatment groups in the signs and symptoms of tuberculosis.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for 6 months vs rifabutin 300 mg daily for 6 months All 3 regimens also included isoniazid daily for 6 months plus ethambutol and pyrazinamide daily for the first 2 months.				
Bock et al.[26] (2002) <u>Stage 1:</u> Rifapentine 900 mg plus isoniazid 15 mg/kg once weekly vs rifapentine 600 mg plus isoniazid 15 mg/kg once-weekly <u>Stage 2:</u> Rifapentine 1,200 mg plus isoniazid 15 mg/kg once-weekly	DB, RCT Patients aged 18 years with culture-confirmed, drug-susceptible pulmonary or extrapulmonary TB and documentation of adequate induction phase therapy	N=150 6 months	Primary: Proportion of subjects that failed to complete study for any reason, including adverse events, intolerance to the medications, clinical or bacteriologic failure, refusal to undergo further study therapy, or withdrawal of consent Secondary: Safety	Primary: Treatment was discontinued in 3 of 52 (6%), 2 of 51 (4%), and 3 of 47 (6%) in the rifapentine 600 mg, 900 mg, and 1,200 mg treatment arms, respectively. Secondary: Only one discontinuation, in the rifapentine 1,200 mg arm, was due to an adverse event possibly associated with study therapy. There was a trend toward more adverse events, possibly associated with study therapy, in the highest-dose arms (P=0.051).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rifapentine 600 mg plus isoniazid 15 mg/kg once-weekly				
Benator et al.[27] (2002) Rifapentine 600 mg plus isoniazid 900 mg once weekly vs rifampin 600 mg plus isoniazid 900 mg twice weekly	MC, OL, RCT Patients 18 years of age or older, who were HIV-negative with pulmonary TB	N=1,004 2 years	Primary: Rates of treatment failure/relapse (defined by positive sputum culture or clinical signs of TB) Secondary: Rate of relapse in patients without cavitation	Primary: Rates of failure/relapse were 46/502 (9.2%) in those on rifapentine once weekly, and 28/502 (5.6%) in those given rifampin twice weekly (P=0.04). Secondary: In patients without cavitation, rates of failure/relapse were 6/210 (2.9%) in the once weekly group and 6/241 (2.5%) in the twice weekly group (P=0.81).
Am Rev Respir Dis.[28] (1977) Streptomycin plus isoniazid plus pyrazinamide given daily vs streptomycin plus isoniazid plus pyrazinamide given 3 times per week vs	RCT Patients with newly diagnosed active pulmonary TB	N=404 30 months	Primary: Rate of treatment failure Secondary: Rate of relapse at 30 months	Primary: The rates of treatment failure at six months were 4%, 1%, and 0% with twice weekly, three times weekly, or daily therapy for patients with drug susceptible isolates. Secondary: The relapse rate at 30 months for patients treated for six months was 21 percent compared to 6 percent for those treated for nine months.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
streptomycin plus isoniazid plus pyrazinamide given twice per week				
Gelband et al.[29] (2000) Streptomycin, isoniazid, rifampin, pyrazinamide administered for <6 months vs streptomycin, isoniazid, rifampin, pyrazinamide administered for >6 months	MA Randomized trials comparing two or more TB drug regimens, in which at least one regimen was <6 months and it was compared with at least one regimen that lasted longer, in patients with active TB	N=4,100 (7 trials) Variable duration	Primary: Relapse rates Secondary: Rate of adverse drug reactions	Primary: Relapse rates were consistently higher after shorter duration treatment regimens. Results were significantly better in the longer duration groups. Secondary: There was little or no difference in the rates of adverse reactions or toxicity requiring a change of regimen or discontinuation of treatment.
Singapore Tuberculosis Service[44] (1991) Streptomycin (SM), isoniazid (INH), rifampin (RIF) and pyrazinamide (PZA) for 2 months	RCT Patients with sputum smear-positive pulmonary tuberculosis	N=310 18 months	Primary: Bacteriologic failures during chemotherapy and relapse at 18 months Secondary: Adverse effects	Primary: Among 271 patients with drug-susceptible strains of tubercle bacilli pretreatment, there were no bacteriologic failures during chemotherapy. Relapse occurred in 7% of patients in the group that received SM and INH/RIF/PZA as a FDC for 2 months and 0% of patients in the group that received the same agents as separate formulations. Relapse occurred in 5% of patients in the group that received SM and INH/RIF/PZA as a FDC for 1 month and 2% of patients in the group that received the same agents as separate formulations. Relapse occurred in 8% of patients in the group that received

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs streptomycin, isoniazid, rifampin and pyrazinamide for 1 month vs isoniazid, rifampin and pyrazinamide for 2 months During the initial period of daily chemotherapy, the patients were also allocated at random to be given their isoniazid, rifampin and pyrazinamide either as a fixed-dose combination (FDC) or as 3 separate formulations.				INH/RIF/PZA as a FDC for 2 months and 2% of patients in the group that received the same agents as separate formulations. The overall relapse rates were higher with the FDC regimens (P=0.04). Secondary: The most common spontaneous complaints were nausea and vomiting reported by 8% of patients receiving the FDC and 7% of patients receiving the drugs in separate formulations.
Treatment of Tuberculosis Infection in HIV-Positive Patients				
Swaminathan et al.[54] (2010) Ethambutol 1,200 mg, isoniazid 600 mg, rifampicin 450-600 mg and pyrazinamide,	OL, MC, RCT HIV-infected patients with newly diagnosed pulmonary or extra-pulmonary tuberculosis	N=327 36 months	Primary: Favorable outcome, recurrence, all-cause mortality	Primary: In the ITT analysis, 83% of patients in the 6-month group and 76% of patients in the 9-month group had a favorable outcome (RR, 1.08; 95% CI, 0.97–1.21; P=0.15). In the PP analysis, there was no difference in favorable outcome at the end of treatment between the two regimens (85% with the 6-month regimen and 78% with the 9-month regimen; P=NS). There was no significant difference between the treatment groups in overall recurrence rates (19% with the 6-month regimen and 13% with the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1,500 mg 3 times/weekly for 2 months, followed by 4 months of isoniazid and rifampicin at the same doses vs ethambutol 1,200 mg, isoniazid 600 mg, rifampicin 450-600 mg and pyrazinamide, 1,500 mg 3 times/weekly for 2 months, followed by 7 months of isoniazid and rifampicin at the same doses				9-month regimen; P=0.2). Overall, 116 deaths (35%) occurred among 327 patients. In the 6-month regimen, 15 deaths occurred during treatment (5 TB, 10 non-TB) and 45 during follow-up (12 TB, 33 non-TB). In the 9-month regimen, there were 19 deaths during treatment (9 TB, 10 non-TB) and 37 (10 TB, 27 non-TB) during the follow-up phase. There was no significant difference in overall mortality between the study regimens: 36 and 35% of patients.
Vernon et al.[31] (1999) Isoniazid 900 mg and rifapentine 600 mg once weekly vs isoniazid 900 mg and rifampin 600 mg twice weekly	MC, OL, RCT HIV-seropositive patients 18 years of age or older with culture-positive pulmonary TB susceptible to isoniazid and rifampin	N=61 16 weeks	Primary: Rate of relapse Secondary: Resistant to a rifamycin (rifabutin, rifampin, or rifapentine)	Primary: Five of 30 patients in the once-weekly isoniazid/rifapentine group relapsed, compared with 3 of 31 patients in the twice-weekly isoniazid/rifampin group (P=0.41). Secondary: Four of 5 relapses in the once-weekly isoniazid/rifapentine group had mono-resistance to rifamycin, compared with 0 out of 3 in the rifampin group (P=0.05).
Murray et al.[32] (1999)	PRO Patients with	N=376 6 months	Primary: Impact of HIV status on drug	Primary: There was no association between HIV status and history of previous TB or drug resistance.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by 4 months of isoniazid and rifampin	sputum culture-positive new or recurrent pulmonary TB diagnosed in 1995 were prospectively enrolled in the cohort		resistance Secondary: Mortality	Treatment interruption rates (2%) and the rate at which patients transferred out of the treatment program (1.6%) were not associated with HIV status. Secondary: Mortality was 0.5% in HIV-negative patients versus 13.7% in HIV-positive patients, and in the latter group was associated with CD4 lymphocyte depletion.
Nettles et al.[33] (2004) Four-drug TB therapy, followed by twice-weekly isoniazid and rifampin vs isoniazid and rifabutin	OBS Patients were included if they had culture-confirmed rifamycin-susceptible tuberculosis	N=108 1 year	Primary: Rates of acquired rifamycin resistance Secondary: Rates of recurrent tuberculosis	Primary: Among the 108 HIV-seropositive patients, 3 (3.7%) of 81 who were treated with rifampin and 0 of 27 who were treated with rifabutin had ARR (acquired rifamycin-resistant) tuberculosis (P=0.57). None of the HIV-seronegative patients or the patients with unknown HIV status developed ARR tuberculosis. Secondary: Among HIV-seropositive patients, the only risk factor for recurrent tuberculosis was a low median initial CD4 T lymphocyte count (51 vs 138 cells/mm^3; P=0.02).
Perriens et al.[40] (1995) Isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) daily for 2 months, followed by INH and RIF twice weekly for 4 months, followed by INH and RIF twice weekly for a further 6 months	PRO, OL HIV-seropositive patients with first episode of pulmonary TB	N=335 24 months	Primary: Rates of relapse at 24 months	Primary: At 24 months, the HIV-seropositive patients who received extended treatment (INH and RIF for 6 months longer) had a relapse rate of 1.9%, as compared with 9% for the HIV-seropositive patients who received placebo for the corresponding 6 months (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs INH, RIF, PZA, and EMB daily for two months, followed by INH and RIF twice weekly for 4 months, followed by placebo twice weekly for a further 6 months				
Treatment of Latent Tuberculosis Infection in HIV-Negative Patients				
Fraser et al.[35] (2006) Study 1 Isoniazid 15-20 mg/kg/day, pyrazinamide 25-35 mg/kg/day, ethionamide 10-15 mg/kg/day and/or ethambutol 15-20 mg/kg/day and/or ofloxacin 15 mg/kg/day Study 2 Isoniazid 400 mg/day	MA Individuals with a sputum culture positive for *Mycobacterium tuberculosis*, which was multi-drug resistant	N=169 (2 trials) 6 months	Primary: Effectiveness of treatment of latent TB infection in patients at risk for developing multidrug resistant TB	Primary: A prospective cohort study found individualized treatment to be effective for preventing active TB in children (OR=0.20, 95% CI: 0.04 to 0.94), while a retrospective cohort study found isoniazid not to be effective (OR=0.46, 95% CI: 0.07 to 2.32).
Hanta et al.[22] (2007) Isoniazid 300 mg daily for 9 months	OL Patients who administered anti-TNFα treatment	N=86 9 months	Primary: Development of hepatotoxicity	Primary: The rate of development of hepatotoxicity among those taking isoniazid was found to be five cases (8.3%), whereas among those who were not given isoniazid, no hepatotoxicity was detected (P=0.317).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(LTBI) vs no tuberculosis treatment (no LTBI present) All patients received active treatment with anti-TNFα therapy	for a rheumatologic disease and were also receiving treatment with isoniazid for latent tuberculosis			Active tuberculosis infection was not encountered in any patient throughout the study period in all groups.
Spyridis et al.[23] (2007) <u>Period 1 (1995-1998)</u> Isoniazid 10 mg/kg once daily for 9 months (group A) vs isoniazid 10 mg/kg and rifampin 10 mg/kg once daily for 4 months (group B) <u>Period 2 (1999-2002)</u> Isoniazid 10 mg/kg and rifampin 10 mg/kg once daily for 4 months (group C)	RCT Children ≤15 years of age with latent tuberculosis infection	N=926 11 years	Primary: Compliance and radiographic findings	Primary: A total of 850 (91.8%) of 926 patients had either excellent or moderate compliance. The rest of the patients had poor compliance either with treatment or with follow-up examinations. Poor compliance was more common for patients initially assigned to group A than for patients in group B (P=0.029). The rate of poor compliance was not significantly different between groups C and D (P=0.533). Of the 32 patients with poor compliance in group A, 17 (53%) either did not return for follow-up examinations after the fourth month or received <80% of total treatment. Among the patients with excellent or moderate compliance, new radiographic findings, such as hilar adenopathy and/or parenchymal lesions suggestive of possible active disease, were seen during follow-up examination 4 months after the initiation of treatment in 48 (24%) of 200 patients in group A, compared with 26 (11.8%) of 220 patients in group B (P=0.001). New radiographic findings were found in 30 (13.6%) of 221 compliant patients in group C and in 23 (11%) of 209 compliant patients in group D (P=0.418). All of these patients were subsequently treated for active disease and received a total of 9 months of treatment with isoniazid and rifampin. All children who participated in the study responded well to treatment, and no cases of clinical TB were documented at the end of therapy and during follow-up.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs isoniazid 10 mg/kg and rifampin 10 mg/kg once daily for 3 months (group D)				Serious drug-related adverse events were not detected in any of the patients participating in the study. Nausea and epigastric pain were reported by 13 (6.5%) of 200 compliant patients in group A, and a transient increase in liver enzyme levels (≤3 times the upper limit of normal) was reported in 12 patients (6%). Of the 650 patients enrolled in the short-term treatment groups, 8 children (1.2%) had a transient increase in liver enzyme levels, 5 (0.7%) reported nausea or epigastric pain, 9 (1.3%) had a transient maculopapular rash, and 5 (0.7%) had a photosensitivity reaction. Discontinuation or modification of treatment was not required in any patient.
Ziakas et al.[49] (2009) Rifampin (RIF) 10 mg/kg/day for 4 months vs isoniazid (INH) 5 mg/kg/day for 9 months	MA Patients with latent tuberculosis infection	N=3,586 (4 trials) 9 months	Primary: Non-completion rates, hepatotoxicity and failures	Primary: Non-completion rates in the RIF arm ranged from 8.6% to 28.4% compared to 24.1% to 47.4% in the INH arm. Among 2,118 patients in the 4 month-RIF arm and 1,468 patients in the 9 month-INH arm, the pooled effect of RIF was protective under the random-effects model (RR, 0.53; 95% CI, 0.44–0.63). Patients in the 4 month-RIF arm had half of the risk of not completing the treatment course than patients in the 9 month-INH arm. Hepatotoxicity rates ranged from 0% to 0.7% in the 4 month-RIF arm and from 1.4% to 5.2% in the 9 month-INH arm. Regarding hepatotoxicity, the pooled effect of 4 month-RIF was also protective under the fixed-effects model (RR, 0.12; 95% CI, 0.05–0.30). There was limited information regarding tuberculosis reactivation in the included studies. The internal validity of the studies included in this meta-analysis is limited by a lack of blinding in two randomized trials and a retrospective design in the other two trials.
Bright-Thomas et al.[52] (2010) Rifampicin (R) and isoniazid (H) prophylaxis for 3 months (3RH)	OBS Children with latent tuberculosis infection (LTBI) who were treated with rifampicin and isoniazid	N=334 Mean 12.35 years	Primary: Proportion and rate of tuberculosis	Primary: Of the 252 patients who were still registered with the local database, 3 (1.19%) patients developed TB. This was 6 months, 6 years 11 months and 7 years 10 months after the commencement of prophylaxis. The three cases of clinical TB occurred during a total of 3,113 years of follow-up. The rate of clinical TB was 0.964/1,000 person-years (95% CI, 0.0199 to 2.816).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No patient developed significant hepatitis on 3RH requiring cessation of treatment during the active treatment period.
Gao et al.[34] (2006) Rifampin 450 mg and pyrazinamide 1,500 mg (<40 kg) or rifampin 450 mg and pyrazinamide 2,000 mg (40-50 kg) or rifampin 600 mg and pyrazinamide 2,500 mg twice weekly (>50 kg) for 2 months vs isoniazid 600 mg and vitamin B6 25 mg (<50 kg) or isoniazid 800 mg and vitamin B6 25 mg (>50 kg) twice weekly for 6 months vs rifampin 600 mg/day and pyrazinamide 3,500 mg twice weekly for 3	MA Studies were included if the study population included in the trials were at high risk of developing active TB	6 trials 12 months	Primary: Development of active TB Secondary: Serious adverse effects and death	Primary: Rates of TB in the rifampin and pyrazinamide group were similar to those in the isoniazid group, whether the subjects were HIV-infected or not (HIV-infected patients P=0.89; non-HIV-infected persons P=0.55). Secondary: There was no difference in mortality between the two treatment groups (HIV-infected patient P=0.53; non-HIV-infected persons P=1.00). Subgroup analyses showed that a higher incidence of all severe adverse events was associated with rifampin plus pyrazinamide than isoniazid among non-HIV-infected persons (P=0.0005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
months vs isoniazid 900 mg twice weekly for 6 months vs rifampin 600 mg/day and pyrazinamide 200 mg/kg/day for 2 months vs isoniazid 300 mg/day and vitamin B6 50 mg/day for 12 months vs rifampin 600 mg/day and pyrazinamide 20 mg/kg/day for 2 months vs isoniazid 300 mg daily for 6 months				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rifampin 450 mg/day and pyrazinamide 1,000 mg/day or 20 mg/kg/day (weight <50 kg) or rifampin 600 mg/day and pyrazinamide 1,500 mg/day or 20 mg/kg/day (weight >50 kg) for 2 months vs isoniazid 300 mg/day for 6 months vs rifampin 10 mg/kg/day (maximum 600 mg/day) and pyrazinamide 25 mg/kg/day or 20 mg/kg/day (maximum 2,000 mg) for 2 months vs isoniazid 5				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/day (maximum 300 mg/day) for 6 months Rifampin and pyrazinamide were used for 2–3 months and compared with standard isoniazid therapy for 6–12 months.				
Menzies et al.[48] (2008) Rifampin 10 mg/kg/day for 4 months vs isoniazid 5 mg/kg/day for 9 months	RCT, OL, MC Patients with a positive tuberculin skin test requiring treatment for latent tuberculosis infection (LTBI)	N=847 9 months	Primary: Frequency of grade 3 or 4 adverse events that resulted in study drug discontinuation Secondary: On-time treatment completion (defined as taking more than 80% of doses within a maximum of 150 days for 4 months of rifampin or 301 days (43 weeks) for 9 months of isoniazid)	Primary: Of the 418 who started rifampin, 7 developed grade 3 or 4 adverse events attributed to study therapy by the independent panel compared with 17 of the 422 patients who started isoniazid (95% CI, -5% to -0.1%; P=0.040). The difference in adverse events was entirely attributable to drug-induced hepatitis, which developed in 3 patients (0.7%) taking rifampin compared with 16 patients (3.8%) taking isoniazid (95% CI, -5% to -1%; P=0.003). Of these, 11 had grade 3 hepatitis and 8 had grade 4 hepatitis. In an analysis restricted to patients who took at least 1 month of therapy, 3 of 389 taking rifampin and 16 of 392 taking isoniazid developed grade 3 or 4 hepatotoxicity (95% CI, -5.5% to -1.1%). Grade 1 or 2 adverse events that resulted in permanent discontinuation of therapy and were judged by the study's independent panel to be related to the study drug were less common and similar in frequency in the 2 regimens. The more common of these problems was rash, which occurred in more patients taking rifampin. Secondary: Of the patients assigned to 4 months of rifampin, 78% completed therapy compared with 60% of patients assigned to 9 months of isoniazid (95% CI, 12% to 24%; P<0.001).
Martinson et al.[55]	OL, RCT	N=1,148	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) Rifapentine 900 mg plus isoniazid 900 mg weekly for 12 weeks vs rifampin 600 mg plus isoniazid 900 mg twice weekly for 12 weeks vs isoniazid 300 mg daily for up to 6 years vs isoniazid 300 mg daily for 6 months (control group)	Adults with HIV infection and a positive tuberculin skin test who were not taking anti-retroviral therapy	Median 4 years	Tuberculosis-free survival Secondary: Adherence to the study regimen, adverse events, discontinuation of study medication for any reason, and mycobacterial drug resistance in patients with tuberculosis	Tuberculosis was diagnosed in 78 patients, of whom 62 (79%) had confirmed tuberculosis, 11 (14%) had probable tuberculosis, and 5 (6%) had possible tuberculosis. The overall incidence of all tuberculosis was 1.9 cases per 100 person-years. There were 66 deaths during the follow-up period, for an overall incidence of 1.6 deaths per 100 person-years. Incidence rates of active tuberculosis or death were 3.1 per 100 person-years in the rifapentine–isoniazid group, 2.9 per 100 person-years in the rifampin–isoniazid group, and 2.7 per 100 person-years in the continuous-isoniazid group, as compared with 3.6 per 100 person-years in the control group (P>0.05 for all comparisons). Secondary: The proportions of patients who reported taking or were observed taking more than 90% of their assigned doses of study medication in the time allotted were 95.7% in the rifapentine–isoniazid group, 94.8% in the rifampin–isoniazid group, and 83.8% in the 6-month–isoniazid group. Patients in the continuous-isoniazid group took isoniazid for 89.1% of the total follow-up time. The median duration of receipt of continuous isoniazid was 3.3 years. There were no deaths attributed to a study drug. A grade 3 or 4 elevation in the aspartate or alanine aminotransferase level occurred during the treatment phase in 1.5%, 2.4%, 28.0%, and 5.5% of patients in the rifapentine–isoniazid, rifampin–isoniazid, continuous-isoniazid, and 6-month–isoniazid groups, respectively (P<0.001 for the comparison of continuous isoniazid with 6-month isoniazid). Drug-susceptibility testing was performed in 58 of 62 *M. tuberculosis* isolates (94%). Two cases of isoniazid-resistant tuberculosis and three cases of rifampin-resistant tuberculosis were detected. Multidrug-resistant tuberculosis (resistance to both isoniazid and rifampin) was detected in 2 of the isolates (3%), 1 from a patient in the rifapentine–isoniazid group and the other from a patient in the continuous-isoniazid group.
Treatment of Latent Tuberculosis Infection in HIV-Positive Patients				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Halsey et al.[38] (1998) Isoniazid 600 mg twice weekly for 24 weeks (<50 kg) or isoniazid 800 mg twice weekly for 24 weeks (≥50 kg) vs rifampin 450 mg with pyrazinamide 1,500 mg twice weekly for 8 weeks (<40 kg) or rifampin 450 mg with pyrazinamide 2,000 mg twice weekly for 8 weeks (40-50 kg) or rifampin 600 mg with pyrazinamide 2,500 twice weekly for 8 weeks (>50 kg)	PRO, RCT Patients 16-77 years old, HIV-1 seropositive, with a positive purified-protein derivative (PPD) skin test, and who had a normal chest radiograph	N=784 4 years	Primary: Risk of TB during first 10 months Secondary: Risk of TB during first 36 months	Primary: Risk of tuberculosis during the first 10 months after entry was 3.7% among patients who received rifampin and pyrazinamide compared with 1.0% (P=0.03) among patients who received isoniazid. Secondary: Risk of tuberculosis at 36 months after entry was 5.4% among patients who received rifampin and pyrazinamide versus 5.1% among patients who received isoniazid (P=0.9).
Woldehanna et al.[37] (2004) Previous therapy (any antituberculosis agent)	MA HIV-positive patients without active tuberculosis	N=8,130 Variable duration	Primary: Effectiveness of TB preventive therapy in reducing the risk of active TB and death	Primary: Preventative therapy was associated with a lower incidence of active TB (RR 0.64, 95% CI: 0.51 to 0.81). In individuals with a positive tuberculin skin test this result was even more pronounced (RR 0.38, 95% CI: 0.25 to 0.57) compared to patients with a negative skin test (RR 0.83 95% CI: 0.58 to 1.18).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				Overall there was no evidence that preventative therapy when compared to placebo reduced all cause mortality (RR 0.95, 95% CI: 0.85 to 1.06).
Ena et al.[36] (2005) Isoniazid for 6-12 months vs rifampin plus isoniazid daily for 3 months	MA Patients with latent TB (both HIV positive and negative patients)	N=1,926 (5 trials) 12 months	Primary: Incidence of TB, side effects requiring drug withdrawal, mortality	Primary: A total of 4.1% of patients in the monotherapy group compared to 4.2% of patients in the combination group developed TB, a difference that was not significant (P=0.083). A total of 4.8% of patients in the monotherapy group compared to 4.9% of patients in the combination group required drug withdrawal due to sever adverse events, a difference that was not significant. A total of 10.4% of patients in the monotherapy group compared to 9.5% of patients in the combination group died during the trail, a difference that was not significant (P=0.36).
Prophylaxis of Tuberculosis Infection in HIV-Positive Patients				
Zar et al.[24] (2007) Isoniazid 10 mg/kg/day daily or three times weekly as prophylaxis vs placebo Sulfamethoxazole-trimethoprim 5 mg/kg/dose (trimethoprim component) was also given to all patients daily or	RCT, DB, PC Children ≥8 weeks with HIV	N=263 Median 5.7 months	Primary: Mortality Secondary: Incidence of tuberculosis, toxicity	Primary: Mortality was lower in the isoniazid group (8%) than in the placebo group (16%; hazard ratio 0.46; 95% CI 0.22 to 0.95). The benefit applied to children across all categories of severity of clinical disease and in all ages. The reduction in mortality was similar in children assigned to isoniazid 3 times/week compared with every day (P=0.943). There were no deaths among children with positive results on tuberculin skin testing. Secondary: The incidence of confirmed or probable tuberculosis was lower in the isoniazid group (4%) than in the placebo group (10%; hazard ratio 0.28; 95% CI, 0.10 to 0.78). The protective effect of isoniazid on incidence of tuberculosis occurred in all categories of severity of clinical disease in children aged >1 year and in both dose regimens. All *M tuberculosis* isolates were sensitive to anti-tuberculosis drugs including isoniazid. The incidence of grade 3 or 4 toxicity was l4% in the isoniazid group and 6.1% in the placebo group. No child required permanent discontinuation

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
three times weekly as prophylaxis for opportunistic infections.				of trial drug. No cutaneous or neurological toxicity was observed.
Madhi et al.[56] (2011) Isoniazid 10 to 20 mg/kg daily vs placebo All infants received trimethoprim-sulfamethoxazole prophylaxis and the BCG vaccine against TB within 30 days after birth.	DB, MC, RCT HIV-infected infants and uninfected infants exposed to HIV during the perinatal period	N=1,352 96 to 108 weeks	Primary: Rate of tuberculosis disease and death in HIV-infected children (TB-disease-free survival); rate of latent tuberculosis infection, tuberculosis disease, and death in HIV-uninfected children (TB-infection-free survival)	Primary: HIV-infected cohort: A total of 274 HIV-infected infants were enrolled in each study group. Either protocol-defined tuberculosis or death occurred in 52 children (19.0%) in the isoniazid group as compared with 53 children (19.3%) in the placebo group (HR, 0.98; 95% CI, 0.67 to 1.44). Tuberculosis accounted for 31 (59.6%) of the primary end points in the isoniazid group and for 38 (71.7%) in the placebo group (P=0.40). Death accounted for 21 (40.4%) and 15 (28.3%) of the primary end points in the two groups, respectively (P=0.12). HIV-uninfected cohort: Eighty-four children (10.4%) reached a primary end point, a composite of tuberculosis disease, latent tuberculosis infection, or death. The estimated hazard ratio for the isoniazid group as compared with the placebo group was 0.85 (95% CI, 0.55 to 1.30). There was no significant difference between study groups (P=0.44).
Samandari et al.[50] (2011) Isoniazid (INH) 300 or 400 mg/day for 6 months (control) vs isoniazid (INH) 300 or 400 mg/day for 36 months	DB, MC, RCT Adults with HIV infection in Botswana	N=1,995 36 months	Primary: Incident tuberculosis Secondary: Death, safety	Primary: Overall, there were 54 incident cases of tuberculosis. Thirty-four (3.4%) patients in the control group and 20 (2.0%) of patients in the long-term isoniazid group had incident tuberculosis. Incidence was 1.26% per year in the control group compared with 0.72% per year in the long-term isoniazid group (HR, 0.57; 95% CI, 0.33–0.99; P=0.047). Tuberculosis incidence in the two groups diverged about 200 days after completion of the initial 6 months' isoniazid prophylaxis, suggesting that the benefit of the initial treatment was lost by this time. Secondary: Mortality was 1.3% per year and did not differ between study groups for all enrolled participants. However, for patients with a positive tuberculin skin test, mortality was three times lower in the long-term isoniazid group than in the control group (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A total of 1% of patients in the control group had severe adverse events associated with study drugs, compared with 1.3% of patients who received long-term isoniazid (P=0.36). There were 6 cases of hepatitis and 1 case of rash in the control group. There were 9 cases of hepatitis, 1 case of rash, and 1 case of peripheral neuropathy in the long-term isoniazid group.
le Roux et al.[51] (2009) Isoniazid 10 mg/kg once daily vs isoniazid 10 mg/kg 3 times/week TMP-SMX prophylaxis was administered on the same dosing schedule as isoniazid	RCT Children >8 weeks with HIV infection	N=324 2 to 4 years	Primary: Adherence	Primary: Similar mean adherence was achieved by the group taking daily medication (93.8%; 95% CI, 92.1-95.6) and by the 3 times/week group (95.5%; 95% CI, 93.8-97.2). Two-hundred and seventeen (78.6%) children achieved a mean adherence of ≥90%. Adherence was similar for the daily and 3 times/week dosing schedules (univariate model: OR, 0.88; 95% CI, 0.66-1.17; P=0.38; multivariate model: OR, 0.85; 95% CI, 0.64-1.11; P=0.23). Age at study visit was predictive of adherence, with better adherence achieved in children >4 years of age (OR, 1.96; 95% CI, 1.16-3.32; P=0.01).

Study abbreviations: CI=confidence interval, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, R=randomized, RCT=randomized controlled trial, RR=relative risk
Class specific abbreviations: ARR: acquired rifamycin-resistant, HIV=human immunodeficiency virus, LTBI=latent tuberculosis infection, TB=tuberculosis
*Rifampicin is the international name for rifampin.
^Not commercially available in the US.

Additional Evidence

Dose Simplification
Several studies have compared the efficacy and safety of the fixed-dose combination (FDC) products to the individual components administered as separate formulations. Four studies reported no difference in efficacy between the treatment arms, while two studies found that the FDC products were associated with an increase in relapse rates.[41-46] There was no difference in the incidence of adverse events in three studies, while a fourth study found that there were fewer reports of gastrointestinal adverse events, visual disturbances and peripheral neuropathy with the use of the FDC product.[41-44] Patient compliance was also assessed; two studies found no difference in compliance with the FDC product, while a third study reported a higher rate of noncompliance with the FDC product compared to the administration of the individual components as separate formulations.[41,43,46]

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 16. Relative Cost of the Antituberculosis Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Aminosalicylic acid	packet	Paser®	$$$$$	N/A
Capreomycin	injection	Capastat Sulfate®	$$$$$	N/A
Cycloserine	capsule	Seromycin®	$$$$$	N/A
Ethambutol	tablet	Myambutol®*	$$$-$$$$	$$-$$$
Ethionamide	tablet	Trecator®	$$$$$	N/A
Isoniazid	injection, syrup, tablet	N/A	N/A	$-$$$
Pyrazinamide	tablet	N/A	N/A	$$
Rifabutin	capsule	Mycobutin®	$$$$$	N/A
Rifampin	capsule, injection	Rifadin®*	$$-$$$$$	$$-$$$$$
Rifampin and isoniazid	capsule	Rifamate®*	$$$$$	$$$$
Rifampin, isoniazid, and pyrazinamide	tablet	Rifater®	$$$$	N/A
Rifapentine	tablet	Priftin®	$$$$	N/A

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

X. Conclusions

The treatment of tuberculosis is a long-term process and focuses on treating active disease, as well as latent infections. The initial phase of treatment kills rapidly multiplying populations of *Mycobacterium tuberculosis*. The recommended treatment regimen during this phase includes isoniazid, rifampin, pyrazinamide and ethambutol to prevent the emergence of drug resistance.[15,19,21] This is followed by a continuation phase, which kills the intermittently dividing populations; rifampin and isoniazid are the preferred treatment options during this phase.[15,19]

Treatment of latent tuberculosis consists of monotherapy for 6-9 months and isoniazid is the preferred agent.[13,16-17,19] The combination of isoniazid and rifapentine (given as directly observed therapy) is as an equal alternative to isoniazid (self-supervised therapy) in patients ≥12 years of age who have a predictive factor for a greater likelihood of TB developing.[58] The preferred regimen for children 2–11 years of age is daily isoniazid. Rifampin is an alternative treatment option for patients who may not tolerate isoniazid; however, potential drug interactions should be considered.[13,16-17,19] Due to reports of severe liver injury and deaths, shorter-course regimens with rifampin and pyrazinamide are not recommended for the treatment of latent tuberculosis infections.[17]

Ethambutol, isoniazid, pyrazinamide, rifampin, and rifampin/isoniazid are available in a generic formulation. There are two fixed-dose combination products that are currently available for the treatment of tuberculosis. The three-drug combination containing rifampin, isoniazid and pyrazinamide is approved for the treatment of pulmonary tuberculosis during the 2-month initial phase. The two-drug combination containing rifampin and isoniazid is approved for the treatment of pulmonary tuberculosis during the continuation phase. Several studies have found no difference in relapse rates, or demonstrated higher relapse rates, with the fixed-dose combination products compared to the individual components administered as separate formulations.[41-46] Available studies do not demonstrate an improvement in patient compliance with the use of fixed-dose combination products.[41,43,46]

Azithromycin and clarithromycin are recommended for the prophylaxis of *Mycobacterium avium* complex disease in adults with AIDS.[20] Rifabutin is also effective, but it is not as well tolerated.[20] Both azithromycin and clarithromycin are available generically.

There is insufficient evidence to support that one brand antituberculosis agent is more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand antituberculosis agents 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 antituberculosis agent 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
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AHFS Class 081692
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I. Overview

Dapsone is approved for the treatment of leprosy and dermatitis herpetiformis.[1-3] Leprosy is a chronic granulomatous infection of the skin, nerves, and eyes caused by *Mycobacterium leprae*.[4] Dapsone was introduced as a treatment for leprosy in the late 1940's and was used extensively as monotherapy. However, bacterial resistance to dapsone became an increasing concern. The World Health Organization has issued official recommendations for multi-drug therapy (MDT) and currently recommends treating patients with leprosy with a combination of anti-infective drugs.[7]

Dermatitis herpetiformis is a cutaneous manifestation of celiac disease, which is characterized by pruritic papulovesicular skin eruptions.[5] While dapsone may be used to treat dermatitis herpetiformis, it is generally used in combination with a lifelong gluten-free diet. Eventually, patients adhering to a gluten-free diet may exhibit a reduced requirement for dapsone, or may be able to discontinue its use completely.

Dapsone is a sulfone antimicrobial. The mechanism of action of the sulfones is similar to sulfonamides, which involves inhibition of folic acid synthesis in susceptible organisms.[1-3] Dapsone is bacteriostatic against *Mycobacterium leprae*; however, the mechanism of action in dermatitis herpetiformis is not fully understood.

The miscellaneous antimycobacterials that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Dapsone is available in a generic formulation. This class was last reviewed in November 2009.

Table 1. Antimycobacterials, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Dapsone	tablet	N/A	dapsone

PDL=Preferred Drug List
N/A=Not available

The miscellaneous antimycobacterials 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 antimycobacterials 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 Antimycobacterials, Miscellaneous[1]

Organism	Dapsone
Mycobacterium leprae	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Antimycobacterials, Miscellaneous

Clinical Guideline	Recommendation(s)

World Health Organization (WHO): **WHO Seventh Expert Committee Report on Leprosy[7] (1998)**	Multibacillary Leprosy
	• Rifampicin 600 mg once per month (supervised) AND
	• Dapsone 100 mg daily (self-administered) AND
	• Clofazimine 300 mg once per month (supervised), or 50 mg daily (self-administered)
	• Therapy duration: 24 months
	Paucibacillary Leprosy (Multiple Lesions)
	• Rifampicin 600 mg once per month (supervised) AND
	• Dapsone 100 mg daily (self-administered)
	• Therapy duration: 6 months
	Paucibacillary Leprosy (Single Skin Lesion)
	• Minocycline 100 mg as a single dose AND
	• Ofloxacin 400 mg as a single dose AND
	• Rifampicin 600 mg as a single dose
	Other Regimens for Special Situations
	• Special regimens are required for individual patients who cannot benefit from rifampicin because of allergy or intercurrent diseases such as chronic hepatitis, or who have been shown to be infected with rifampicin-resistant *M. leprae*.
	• Regimen 1:
	  o Clofazimine 50 mg daily AND
	  o Ofloxacin 400 mg daily AND
	  o Minocycline 100 mg daily
	  o Treatment duration: 6 months
	• Regimen 2:
	  o Clofazimine 50 mg daily AND
	  o Minocycline 100 mg daily or ofloxacin 400 mg daily
	  o Treatment duration: 18 months

U.S. Department of Health and Human Services Health Resources and Services Administration (HRSA): **National Hansen's Disease (Leprosy) Program[23]**	General Considerations
	• National Hansen's Disease Program (NHDP) recommendations are for daily rifampin, and for longer duration of treatment than the WHO recommendations, largely due to WHO's cost considerations for developing countries. Treatment that is more intensive and of longer duration is medically preferable.
	Treatment Regimens
	• Adults: Tuberculoid (WHO classification Paucibacillary)
	  o Dapsone 100 mg daily AND
	  o Rifampicin 600 mg daily
	  o Treatment duration: 12 months
	• Children: Tuberculoid (WHO classification Paucibacillary)
	  o Dapsone 1 mg/kg/day AND
	  o Rifampicin 1-2 mg/kg/day
	  o Treatment duration: 12 months
	• Adults: Lepromatous (WHO classification Multibacillary)
	  o Dapsone 100 mg daily AND
	  o Rifampicin 600 mg daily AND
	  o Clofazimine 50 mg daily
	  o Treatment duration: 24 months
	• Children: Lepromatous (WHO classification Multibacillary)

Clinical Guideline	Recommendation(s)
	○ Dapsone 1 mg/kg/day AND ○ Rifampicin 1-2 mg/kg/day AND ○ Clarithromycin 7.5 mg/kg/day ○ Treatment duration: 24 months Alternative Antimicrobial Agents • Minocycline 100 mg daily can be used as a substitute for dapsone in individuals who do not tolerate this drug. It can also be used instead of clofazimine, although evidence of the efficacy of its anti-inflammatory activity against Type 2 reactions is not as substantial as the evidence for clofazimine. • Clarithromycin 500 mg daily is also effective against *M. leprae* and can be used as a substitute for any of the other drugs in a multiple drug regimen. In children, this drug is recommended in place of clofazimine, since clofazimine cannot be used in children in the United States. • Ofloxacin 400 mg daily may also be used in place of clofazimine for adults. This is not recommended for children.
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[8] (2008)**	Primary Prophylaxis of *Pneumocystis (carinii) jiroveci* Pneumonia (PCP) • Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic agent. • If TMP-SMX cannot be tolerated, prophylactic regimens that can be recommended as alternatives include dapsone, dapsone plus pyrimethamine plus leucovorin, aerosolized pentamidine, and atovaquone. • For patients seropositive for *Toxoplasma gondii* who cannot tolerate TMP-SMX, recommended alternatives to TMP-SMX for prophylaxis against both PCP and toxoplasmosis include dapsone plus pyrimethamine plus leucovorin or atovaquone with or without pyrimethamine plus leucovorin. Treatment of *Pneumocystis (carinii) jiroveci* Pneumonia (PCP) • TMP-SMX is the treatment of choice. • Alternative therapeutic regimens for mild-to-moderate disease include dapsone and TMP, primaquine plus clindamycin, and atovaquone. • Patients who have a history of PCP should be administered chemoprophylaxis for life with TMP-SMX unless immune reconstitution occurs as a result of ART. For patients who are intolerant of TMP-SMX, alternatives include dapsone, dapsone combined with pyrimethamine, atovaquone, or aerosolized pentamidine. 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.
World Gastroenterology Organization (WGO): **Practice Guideline: Celiac Disease[6] (2007)**	• Dermatitis herpetiformis is treated with a gluten-free diet and medication to control the rash. • Treatment regimens include dapsone or sulfapyridine. • Treatment may last for several years.

Clinical Guideline	Recommendation(s)
American Gastroenterological Association (AGA): **Medical Position Statement on the Diagnosis and Management of Celiac Disease**[9] **(2006)**	• Treatment of celiac disease requires a strict, lifelong adherence to a gluten-free diet. • This is also the case for patients with dermatitis herpetiformis.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antimycobacterials 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 Antimycobacterials, Miscellaneous[1-3]

Indication	Dapsone
Dermatitis herpetiformis	✔
Leprosy	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antimycobacterials are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Antimycobacterials, Miscellaneous[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Dapsone	86-104	70-90	Liver	Renal (85)	10-50

V. Drug Interactions

Significant drug interactions with the miscellaneous antimycobacterials are listed in Table 6.

Table 6. Significant Drug Interactions with the Antimycobacterials, Miscellaneous[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Dapsone	2	Rifamycins	Plasma concentrations and pharmacologic effects of dapsone may be decreased by rifamycins. The antimicrobial effectiveness of dapsone may be reduced.
Dapsone	2	Trimethoprim	Increased serum concentrations of trimethoprim and dapsone may lead to a greater risk of toxicity with each drug.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antimycobacterials are listed in Table 7. Fatal cases of agranulocytosis, aplastic anemia and other blood dyscrasias have been reported with dapsone.[1-3] Serious dermatologic reactions (including toxic epidermal necrolysis) are rare, but potential complications of sulfone therapy.

Table 7. Adverse Drug Events (%) Reported with the Antimycobacterials, Miscellaneous[1-3]

Adverse Reactions	Dapsone
Central Nervous System	
Fever	✔
Headache	✔
Insomnia	✔
Peripheral neuropathy	✔
Psychosis	✔
Vertigo	✔
Dermatological	
Bullous dermatitis	✔
Erythema nodosum	✔
Exfoliative dermatitis	✔
Morbilliform and scarlatiniform reactions	✔
Phototoxicity	✔
Stevens-Johnson syndrome	✔
Toxic epidural necrolysis	✔
Urticaria	✔
Gastrointestinal	
Abdominal pain	✔
Nausea	✔
Pancreatitis	✔
Vomiting	✔
Genitourinary	
Albuminuria	✔
Male infertility	✔
Nephrotic syndrome	✔
Renal papillary necrosis	✔
Hematological	
Agranulocytosis	✔
Anemia	✔
Hemolysis	>10
Hemoglobin decreased	>10
Leukopenia	✔
Methemoglobinemia	>10
Pure red cell aplasia	✔
Red cell life span shortened	>10
Reticulocyte count increased	2-12
Hepatic	
Cholestatic jaundice	✔
Hepatitis	✔
Respiratory	
Interstitial pneumonitis	✔
Pulmonary eosinophilia	✔
Other	
Blurred vision	✔
Drug-induced lupus erythematosus	✔
Hypoalbuminemia	✔

Adverse Reactions	Dapsone
Mononucleosis-like syndrome	✔
Motor loss/muscle weakness	✔
Tachycardia	✔
Tinnitus	✔

✔ Percent not specified

VII. Dosing and Administration

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

Table 8. Usual Dosing Regimens for the Antimycobacterials, Miscellaneous[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Dapsone	Dermatitis Herpetiformis: Initial: 50 mg once daily; maintenance, 50 to 300 mg once daily Leprosy: 100 mg daily with one or more other anti-leprosy drugs	Dermatitis Herpetiformis: Initial and maintenance dose schedule is the same as in adults, but administered at "correspondingly smaller doses" Leprosy: "correspondingly smaller doses" than adults with one or more other anti-leprosy drugs	Tablet: 25 mg 100 mg

VIII. Effectiveness

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

Table 9. Comparative Clinical Trials with the Antimycobacterials, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatitis Herpetiformis				
Fry et al.[16] (1982) Dapsone 100 mg QD plus a gluten-free diet vs dapsone 100 mg QD plus a normal diet	RCT Patients between the ages of 15 and 64 years presenting with dermatitis herpetiformis and IgA deposits in the dermal papillae of uninvolved skin	N=78 3-14 years of follow-up	Primary: Medication discontinuation, dose reduction, macroscopic intestinal abnormality, intra-epithelial lymphocyte count, adverse effects	Primary: While 71% of patients adhering to the gluten-free diet were able to discontinue their medication, only 14% of patients maintained on the normal diet were able to stop therapy. Furthermore, 96% of patients on a strict gluten-free diet were able to stop dapsone or equivalent. On average, it took 8 months to reduce the drug dose and 29 months to discontinue therapy in patients adhering to the gluten-free diet. The incidence of an abnormal intestinal biopsy decreased from 69% to 15% in patients on the gluten-free diet. The mean intra-epithelial lymphocyte count decreased significantly from 393 ± se 28 to 218 ± se 18 in patients maintained on the gluten-free diet; while, the change in the regular diet group was not statistically significant. Side effects occurred in 26% of patients on dapsone therapy.
Leprosy				
Cellona et al.[10] (1990) Dapsone 100 mg QD for 5 years and rifampin 1,200 mg single dose (Group IA) vs dapsone 100 mg QD for 5 years and	RCT Patients aged 15 to 60 years with new onset or relapsed leprosy, with an average bacterial index of at least 4	N=358 5 years	Primary: Clinical improvement assessed every 6 months for the first 2 years and then once a year for the remainder of the study, BI, change in biopsy index, toxicity, tolerability	Primary: Clinical improvement was observed in 78%-94% of patients allocated to Group I at 6 months of therapy and at 1 year, rates of clinical improvement had increased to 92%-100%, reaching and staying at 100% after 4 years of therapy. The difference between the four Group I regimens was not statistically significant. Clinical improvement was observed in 80%-93% of patients allocated to group II at 6 months of therapy, and at 1 year, rates of clinical improvement had increased to 90%-100%, reaching and staying at 100% after 2 years of therapy. The difference between the four Group II regimens was not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rifampin 600 mg QD for 4 weeks (Group IB) vs dapsone 100 mg QD for 5 years and rifampin 1,200 mg single dose and clofazimine* 100 mg TIW for 24 weeks (Group IC) vs dapsone 100 mg QD for 5 years and rifampin 1,200 mg single dose and prothionamide* 375 mg QD for 8 weeks (Group ID) Clofazimine* 100 mg TIW for 5 years and rifampin 600 mg QD for 4 weeks (Group IIA) vs clofazimine* 100 mg TIW for 5 years and rifampin 600 mg QD for 2				No significant differences were observed among the various regimens in terms of reduction in the bacterial index and change in biopsy index. Toxicity was only observed in patients on prothionamide and rifampin therapy. Clofazimine-containing regimens were associated with skin pigmentation in some patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks (Group IIB) vs clofazimine* 100 mg TIW for 5 years and rifampin 1,200 mg once every 4 weeks for 24 weeks (Group IIC) vs rifampin 600 mg QD for 4 weeks, then 600 mg for 2 days every month for 5 years and prothionamide* 375 mg QD for 8 weeks, then thiacetazone* 150 mg QD for 5 years (Group IID)				
THELEP Controlled Clinical Drug Trials[11] (1987) Dapsone 100 mg QD, rifampin 600 mg QD, and prothionamide* 500 mg QD for 2 years (A_2)	MC, RCT Patients with leprosy previously untreated, without detectable dapsone or its metabolites in the urine	N=215 39 months	Primary: *M leprae* persistence, BI	Primary: *M leprae* persistence did not differ between the centers or treatment groups; *M leprae* was detected in 9% of all skin biopsy samples. This finding was consistent at all evaluated time intervals (3, 12, and 24 months). After 3-month treatment with the combined regimens, the mean BI from the examined samples was 4.42.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs dapsone 100 mg QD for 2 years and rifampin as a single 1,500 mg dose (C) vs dapsone 100 mg QD for 2 years, rifampin 900 mg once weekly, and prothionamide* 500 mg QD for 3 months (E_2) vs dapsone 100 mg QD, rifampin 600 mg QD, and clofazimine*100 mg QD for 2 years (A_1) vs dapsone 100 mg QD for 2 years, rifampin as a single 1,500 mg dose, and clofazimine*100 mg QD for 3 months (D_1)				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Villahermosa et al.[12] (2004) Dapsone 100 mg QD and clofazimine* 50 mg QD (unsupervised) plus rifampin 600 mg and clofazimine* 300 mg once monthly (supervised), all for 24 months (MDT Regimen) vs rifampin 600 mg, ofloxacin 400 mg, and minocycline 100 mg once monthly (supervised) for 24 months (ROM Regimen)	RCT Patients from 16 to 60 years of age diagnosed with multi-bacillary leprosy, diagnosed by the presence of at least one of six smear sites having a bacterial index greater than 1, and having a histologic diagnosis of borderline or lepromatous leprosy	N=21 24 months	Primary: Cumulative improvement in lesion scores, bacterial indices, histology, toxicity	Primary: There was a comparable degree of lesion improvement, assessed by cumulative lesion scores, between patients treated with MDT and ROM regimens, 22 and 20, respectively. Both MDT and ROM regimens were safe, tolerable, and caused similar improvement in bacterial indices, and histology. While all MDT-treated patients developed clofazimine-induced pigmentation, none of the patients in the ROM group developed this adverse event.
Dietrich et al.[13-14] (1986, 1994) Dapsone 100 mg QD (Group A) vs dapsone 100 mg QD and rifampin	MC, RCT Patients between the ages of 14 and 60 years with a diagnosis of borderline or lepromatous leprosy, not receiving treatment	N=307 5 years of follow-up	Primary: Therapeutic response, bacterial indices, leprosy reaction	Primary: There was no significant difference between the groups in the therapeutic response to therapy. Groups A, B, and C experienced either a regression (85%, 94%, or 87%, respectively) or a stabilization of their disease during the 3-year treatment period (15%, 6%, or 13%, respectively). A leprosy reaction occurred in an average of 49% of patients enrolled in the study. There was no difference in the bacteriological index reduction between the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
600 mg QD (Group B) vs rifampin 600 mg QD, prothionamide* 350 mg QD, isoniazid 350 mg QD, and dapsone 100 mg QD (Group C)	for at least 4 weeks before study entry			study groups. During the 10 years of the study, there were no significant differences in the following lab values between the study groups: hemoglobin, leukocyte count, alanine aminotransferase, aspartate aminotransferase, total protein, and blood urea.
Smith et al.[15] (2000) Dapsone 20-300 mg weekly to twice weekly or acedapsone* 125-225 mg via an intramuscular injection every 75 days	MA Randomized or non-randomized trials evaluating chemoprophylaxis with dapsone or acedapsone	N=20,076 (14 trials)	Primary: Disease prevention	Primary: There was a significant reduction in the risk of acquiring leprosy in patients receiving a prophylactic regimen compared to placebo (RR 0.40; 95% CI, 0.29 to 0.55).
Kroger et al.[24] (2008) <u>Adults</u> Dapsone 100 mg daily and clofazimine 50 mg daily (unsupervised); rifampicin 600 mg and clofazimine 300 mg once every 4 weeks	OL Newly detected and treatment-naive leprosy patients	N=2,912 5 years	Primary: Relapse rate and adverse events	Primary: Twenty-seven patients developed new lesions. Of these, 11 developed new lesions during treatment and the remaining 16 during follow-up. Of these 27 patients, 21 developed new lesions on account of reactions. Six patients were clinically compatible with relapse. Three of these relapses occurred in the first year, two were reported during the second year and one patient developed relapse in the third year of follow-up. All these patients were assessed as 'lesion inactive' at the completion of treatment. Subsequently they developed new lesions, and were given another course of U-MDT, and are being followed up. There were 55 reaction episodes (38 type 1 and 17 type 2 reactions). Of these, 23 occurred during the treatment phase, the remaining 29 occurred

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(supervised) for 6 months Children (10–14 years) Dapsone 50 mg daily and clofazimine 50 mg every other day (unsupervised); rifampicin 450 mg and clofazimine 150 mg once every 4 weeks (supervised) for 6 months Children (<10 years) Dapsone 1-2 mg/kg daily and clofazimine 1-2 mg/kg daily (unsupervised); rifampicin 10-20 mg/kg (supervised) for 6 months				afterwards. Thirty-nine neuritis events were reported, of which 16 occurred along with reactions. Eleven patients reported neuritis during the treatment phase, 13 patients reported adverse drug reactions. Of these 13 events, 11 were due to dapsone (seven had exfoliative dermatitis and four had non-specific dermatitis). One patient reported hepatitis whose cause was not known. One patient developed mononucleosis. All 21 reported deaths were due to causes other than leprosy and were unrelated to U-MDT. Approximately 99% (n=2,480) of patients completed treatment within the stipulated period. Of these, 19% were assessed as 'lesion inactive', 78% as 'improved', 3% as static and 0.2% as deteriorated at completion of treatment. The proportion with inactive lesions among PB patients was greater than among MB patients (27% vs 6%; P<0.001) in this group. A total of 2284 patients were due for first year followup; 16 were lost and 2013 (88%) patients completed first year follow-up. Of these, 1004 (49%) were classified as 'lesion inactive', 996 (49%) as 'improved' and 0.6% as 'static'. Amongst those who completed the first year of follow-up after treatment, the proportion with inactive lesions was higher for PB than MB patients (59% vs 37%; P<0.001). Of the patients due for second year follow-up after treatment, 807 patients (51%) completed follow-up, in whom the proportion with inactive lesions was 57% in PB and 28% in MB patients (P<0.001).
Prophylaxis of *P jiroveci* Pneumonia (PCP) and Toxoplasmosis				
El-Sadr et al.[19] (1998) Dapsone 100 mg QD vs atovaquone 1,500	MC, OL, RCT Patients ≥13 years old with a history of PCP, or with a CD4 cell count no higher than 200 per mm^3 or no more than 15% of the total	N=1,057 Mean 27 months	Primary: Onset of probable or micro-biologically confirmed PCP Secondary: Confirmed or probably	Primary: There was no statistically significant difference in PCP development between the dapsone- and atovaquone-treated groups (RR, 0.85; 95% CI: 0.67 to 1.09; P=0.20). Secondary: There was no statistically significant difference in toxoplasmosis development between the dapsone- and atovaquone-treated groups (RR, 1.18; 95% CI: 0.26 to 5.30; P=0.83).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD	lymphocyte count, and a history of treatment-limiting reaction to sulfonamides or trimethoprim		toxoplasmosis, death, combined end point of death or PCP, discontinuation of the drug due to intolerable adverse events	There was no statistically significant difference in mortality between the dapsone- and atovaquone-treated groups (RR, 1.07; 95% CI: 0.89 to 1.30; P=0.45). There was no statistically significant difference in the cumulative endpoint between the two groups (RR, 0.98; 95% CI: 0.89 to 1.16; P=0.80). There was no statistically significant difference in the number of patients discontinuing treatment because of intolerable toxicity between the two groups (RR, 0.94; 95% CI: 0.74 to1.19; P=0.59). Among patients receiving a dapsone-based prophylactic regimen at baseline, the risk of discontinuation due to adverse effects was higher in the atovaquone group (RR, 3.78; 95% CI: 2.37 to 6.01; P<0.001). Among patients not receiving a dapsone-based prophylactic regimen at baseline, the risk of discontinuation due to adverse effects was lower in the atovaquone group (RR, 0.42; 95% CI: 0.30 to 0.58; P<0.001).
Payen et al.[20] (1997) Dapsone 50 mg QD vs pyrimethamine-sulfadoxine once weekly	OL, PRO, RCT HIV-positive patients with a CD4 cell count no higher than 200 per mm^3 or 20% of the total lymphocyte count	N=209 Mean 533 days	Primary: Onset of PCP (confirmed by pneumopathy and *P jiroveci* cysts isolated at induced sputum, broncho-alveolar lavage, or transbronchial biopsy), intolerable adverse events, and death	Primary: There were no statistically significant differences between the two prophylactic regimens in any of the evaluated primary endpoints (P>0.1). Secondary: There were no statistically significant differences between the two prophylactic regimens in any of the evaluated secondary endpoints (P>0.1).
Ioannidis et al.[17] (1996) Dapsone vs	MA Randomized trials comparing dapsone, aerosolized pentamidine, or SMX-TMP in adult	N=6,583 (35 trials) Variable duration	Primary: Number of *P jiroveci* episodes, *P jiroveci*-related deaths, toxoplasmosis episodes, all-cause	Primary: There was a significant decrease in the incidence of *P jiroveci* events in patients on any primary or secondary prophylactic regimen compared to placebo (RR 0.39; 95% CI, 0.27 to 0.55 and RR 0.16; 95% CI, 0.08 to 0.35, respectively). There was no significant difference in mortality between the different

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pentamidine (aerosolized) vs SMX-TMP vs placebo	patients directly or with placebo		mortality	prophylactic regimens in all 35 trials. Oral prophylactic regimens were significantly more effective in reducing *P jiroveci* events compared to aerosolized pentamidine (RR, 0.39; 95% CI: 0.27 to 0.55). Oral prophylactic regimens were significantly more effective in reducing toxoplasmosis events compared to aerosolized pentamidine (RR, 0.67; 95% CI: 0.50 to 0.88). There was no statistically significant difference in the occurrence of *P jiroveci* and toxoplasmosis events between patients receiving SMX-TMP or dapsone-based regimens (RR, 0.61; 95% CI: 0.34 to 1.10 and 1.26; 95% CI: 0.68 to 2.34, respectively). While SMX-TMP exhibited greater efficacy in reducing *P jiroveci* events (RR, 0.58; 95% CI: 0.45 to 0.75), dapsone-based regimens were comparable to the aerosolized pentamidine regimen (RR, 0.93; 95% CI: 0.72 to 1.19). Compared with aerosolized pentamidine, oral regimens were overall 5 times more likely to be discontinued due to adverse events (RR, 5.38; 95% CI: 3.69 to 7.83). There was no significant difference between the SMX-TMP and dapsone-based regimens in the patient attrition rate as a result of treatment-related adverse effects (RR, 1.30; 95% CI: 1.04 to 1.62). SMX-TMP-treated groups exhibited the smallest prophylaxis failure rates, 0.5% for both primary and secondary prophylaxis.
Bucher et al.[18] (1997) Dapsone vs	MA Randomized, placebo-controlled, intention-to-treat trials comparing dapsone, dapsone-	N=4,870 (22 trials) Variable duration	Primary: Opportunistic infections with PCP, *Toxoplasma* encephalitis, or both, mortality, drug-limiting	Primary: Compared to aerosolized pentamidine, dapsone-based regimens were more effective in preventing PCP events (RR, 0.90; 95% CI: 0.71 to 1.15) but not significantly different in terms of *Toxoplasma* encephalitis prevention (RR, 0.78; 95% CI: 0.55 to 1.11). Compared to dapsone-based regimens, SMX-TMP was more effective in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dapsone-pyrimethamine vs pentamidine, aerosolized vs SMX-TMP	pyrimethamine, aerosolized pentamidine or SMX-TMP		toxicity requiring a change in therapy	preventing PCP events (RR, 0.49; 95% CI: 0.26 to 0.92) but not significantly different in terms of *Toxoplasma* encephalitis prevention (RR, 1.17; 95% CI: 0.68 to 2.04). SMX-TMP was significantly more effective compared to aerosolized pentamidine in preventing PCP events (RR, 0.59; 95% CI: 0.45 to 0.76). Drug-limiting toxicity was experienced by 29.7% of patients treated with a dapsone-based regimen, 6.8% of patients treated with aerosolized pentamidine, and 31.5% of patients on SMX-TMP therapy. There was no significant difference in mortality between the dapsone-based regimen and SMX-TMP (RR, 0.98; 95% CI: 0.80 to 1.08, P>0.20) or the aerosolized pentamidine regimen (RR, 1.07; 95% CI: 0.90 to 1.27, P>0.18). The mortality risk ratio in patients with CD4 cell count <100 cells/mm^3 treated with SMX-TMP compared with dapsone-based regimen was 0.43 (95% CI: 0.21 to 0.88). Mortality was lower in the SMX-TMP-treated group compared with patients on the aerosolized pentamidine therapy (RR, 0.88; 95% CI: 0.74 to 1.06, P=0.04).
Treatment of *P jiroveci* Pneumonia (PCP)				
Safrin et al.[21] (1996) Dapsone 100 mg QD plus trimethoprim (weight-based) vs clindamycin 600 mg TID plus primaquine base	DB, MC, R Patients >13 years old infected with HIV, weighing 35 to 100 kg, with signs of PCP	N=181 Mean 21 days	Primary: Survival (60 days after discontinu-ation of therapy), discontinuation of therapy due to treatment-related adverse effects, therapeutic failure at day 7 and 21 (defined by either an increase in PAO_2-PaO_2 of	Primary: There were no significant differences between the groups in either 7-day or 21-day failure rates (P>0.2). Time to therapeutic failure did not significantly differ between the groups (P>0.2). Mortality rate as well as survival during therapy and for at least 2 months after therapy discontinuation did not significantly differ between the groups (P>0.2). Drug-limiting toxicity was experienced by 36% of patients on SMX-TMP therapy, 24% of patients treated with a dapsone-based regimen, and 33%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
30 mg QD vs SMX-TMP (weight-based)			greater than 20 mm Hg over baseline and persistent signs and symptoms, change of therapy due to toxicity, intubation, or death)	of patients treated with clindamycin-primaquine (P=0.2). Elevation of aminotransferase levels to >5 times the upper limit of normal was more frequently observed in the SMX-TMP group compared with the dapsone-TMP, and clindamycin-primaquine groups (19%, 3%, and 7%, respectively; P<0.003). Serious hematological toxicities occurred more often in the clindamycin-primaquine group compared with the SMX-TMP and dapsone-TMP recipients (28%, 11%, and 12%, respectively; P=0.01). Anemia occurred more often in the clindamycin-primaquine group compared with the SMX-TMP and dapsone-TMP groups (10%, 5%, and 5%, respectively; P=0.2)
Medina et al.[22] (1990) Dapsone 100 mg QD plus trimethoprim 20 mg/kg QD vs SMX 100 mg/kg QD plus TMP 20 mg/kg QD	MA Patients with AIDS and mild-to-moderately-severe new onset PCP, and whose room air PAO_2-PaO_2 was 60 mm Hg or greater	33 trials Mean 21 days	Primary: Therapeutic failure, discontinuation of therapy due to treatment-related adverse effects	Primary: Treatment failure was observed in 3 patients treated with SMX-TMP and 2 patients on dapsone-based regimen (P>0.3). More patients in the SMX-TMP group (57%) required a change of therapy due to intolerable adverse effects compared with the dapsone-based regimen group (30%; P<0.025).

*****Not commercially available in the US.
Drug regimen abbreviations: QD=once daily, TID=three times daily, TIW=three times weekly
Study abbreviations: CI=confidence interval, MA=meta-analysis, MC=multicenter, PRO=prospective, OL=open-label, R=randomized, RCT=randomized controlled trial, RR, risk ratio/relative risk
Miscellaneous abbreviations: BI=bacterial index, MDT=multi-drug therapy, PCP=*Pneumocystis carinii* pneumonia, SE=standard error

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 Antimycobacterials, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Dapsone	tablet	N/A	N/A	$$-$$$

N/A=Not available

X. Conclusions

Dapsone is approved for the treatment of leprosy and dermatitis herpetiformis. It is available in a generic formulation. Dapsone has been shown to be effective for the treatment of leprosy as monotherapy and in combination with other agents.[10-14,24] However, due to the spread of bacterial resistance, the World Health Organization and the National Hansen's Disease Program no longer recommend dapsone monotherapy.[7,23] Both organizations recommend the use of dapsone in combination with one or more other anti-infective agents.[7,23]

Dermatitis herpetiformis is a cutaneous manifestation of celiac disease and it is treated with a gluten-free diet.[6,9] Dapsone has also been used to control the rash associated with dermatitis herpetiformis. There were no comparative clinical trials found in the medical literature evaluating the use of dapsone for the treatment of dermatitis herpetiformis. However, one study reported that patients on a gluten-free diet were able to reduce the dose of dapsone following 8 months of therapy and discontinue treatment after 29 months.[16]

Guidelines for the prevention and treatment of opportunistic infections in patients with HIV recommend trimethoprim-sulfamethoxazole (TMP-SMX) as the treatment of choice for *Pneumocystis jiroveci* pneumonia

(PCP) and *Toxoplasma* encephalitis.[8] Dapsone has a similar spectrum of activity as the sulfonamides and it is recommended as an alternative treatment option for patients who cannot tolerate TMP-SMX.[8] Clinical trials have demonstrated similar efficacy with dapsone and TMP-SMX.[17-18,21-22]

Therefore, all brand miscellaneous antimycobacterials 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 antimycobacterial 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Adamantanes
AHFS Class 081804
May 9, 2012

I. Overview

Influenza A viruses (primarily H1N1 and H3N2) and influenza B viruses circulate worldwide. Influenza epidemics occur nearly every year making this disease a major cause of respiratory illness in the United States.[6] The majority of complications, hospitalizations and deaths from seasonal influenza occur in persons over 65 years old, children younger than 2 years old, and persons of any age with certain underlying health conditions. The most effective way to minimize the negative impact of influenza is through annual vaccination. According to the 2011 recommendations of the Advisory Committee on Immunization Practices (ACIP), annual influenza vaccination is recommended for everyone over 6 months of age.[7]

Antiviral medications are an important adjunct to vaccination for the control and prevention of influenza disease. The adamantanes inhibit two stages of viral replication by interfering with the influenza A M2 protein.[1-3] The M2 protein plays an important role in the uncoating of the infecting virus particle, as well as regulation of the ion channels. Although clinical trials have shown that the adamantanes are effective for the treatment and chemoprophylaxis of influenza, these agents have become less useful in recent years due to the development of resistant strains of influenza A virus.[9-10] Another limitation to the use of adamantanes is that they only have activity against influenza A viruses.[1-3]

Amantadine is also approved for the treatment of parkinsonism and drug-induced extrapyramidal reactions.[1-3] The mechanism of action of amantadine in the treatment of Parkinson's disease and drug-induced extrapyramidal reactions is not known. Data from earlier studies suggest that it may have direct and indirect effects on dopamine neurons. More recent studies have demonstrated that amantadine is a non-competitive NMDA receptor antagonist.

The adamantanes that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Amantadine and rimantadine are available in a generic formulation. This class was last reviewed in November 2009.

Table 1. Adamantanes Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amantadine	capsule, syrup, tablet	N/A	amantadine
Rimantadine	tablet	N/A	rimantadine

PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the adamantanes are summarized in Table 2.

Table 2. Treatment Guidelines Using the Adamantanes

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention (CDC): **Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP)[11]**	General Considerations • During most influenza seasons, rates of serious illness and death are highest among persons aged ≥65 years, children aged <2 years, and persons of any age who have medical conditions that place them at increased risk for complications from influenza. • Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. • All persons aged ≥6 months are recommended for annual influenza

Clinical Guideline	Recommendation(s)

(2011)	vaccination.
	• Antiviral medications are effective for the prevention of influenza and can reduce the duration and severity of illness.
	• The selection of antiviral medications should be based on influenza antiviral resistance patterns, local, state, and national influenza surveillance information on influenza virus type or influenza A virus subtype, the characteristics of the person who is ill, and results of influenza testing if testing is done.
	• Empiric antiviral treatment often is required to avoid treatment delays.
	• Antiviral treatment is recommended as soon as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness or who require hospitalization.
	• Antiviral treatment also may be considered on the basis of clinical judgment for any outpatient with confirmed or suspected influenza who does not have known risk factors for severe illness if treatment can be initiated within 48 hours of illness onset.
	• Oseltamivir or zanamivir are the primary antiviral agents recommended for the prevention and treatment of influenza. Oseltamivir may be used for treatment or chemoprophylaxis of influenza among infants aged <1 year when indicated.
	• Resistance among influenza A (H3N2) virus strains has made amantadine and rimantadine less useful clinically. Circulating 2009 H1N1 virus strains are resistant to the adamantanes. Therefore, amantadine and rimantadine are not recommended for antiviral treatment or chemoprophylaxis of currently circulating influenza A virus strains.
	<u>Treatment Indications</u>
	• Antiviral treatment is recommended as soon as possible for all persons with suspected or confirmed influenza requiring hospitalization or who have progressive, severe or complicated illness regardless of previous health or vaccination status.
	• Empiric antiviral treatment is often necessary, and providers should not delay initiation of treatment while awaiting confirmatory diagnostic tests results or if specimens are not obtained.
	• Among outpatients, antiviral treatment with a neuraminidase inhibitor is recommended for all persons with suspected or confirmed influenza who are at higher risk for influenza complications because of age or underlying medical conditions.
	• Persons at higher risk for influenza complications who are recommended for antiviral treatment for suspected or confirmed influenza include:
	  o Children aged <2 years
	  o Adults aged ≥65 years;
	  o Persons with chronic pulmonary, cardiovascular, renal, hepatic, hematological, metabolic disorders or neurologic and neurodevelopment conditions
	  o Persons with immunosuppression
	  o Women who are pregnant or postpartum
	  o Persons aged <19 years who are receiving long-term aspirin therapy
	  o American Indians/Alaska Natives
	  o Persons who are morbidly obese
	  o Residents of nursing homes and other chronic-care facilities
	• The benefits of antiviral treatment are likely to be greatest if treatment is started as soon as possible after illness onset, and evidence for

Clinical Guideline	Recommendation(s)
	benefit is strongest in studies in which treatment was started within 48 hours of illness onset. • Treatment of any person with confirmed or suspected influenza who requires hospitalization is recommended, even if the patient presents >48 hours after illness onset. • Treatment also can be considered for outpatients with uncomplicated, suspected, or confirmed influenza who are not known to be at increased risk for developing severe or complicated illness if antiviral treatment can be initiated within 48 hours of illness onset. • Persons with influenza who present with an uncomplicated febrile illness typically do not require treatment unless they are at higher risk for influenza complications, but early empiric antiviral treatment of these patients also might provide benefit (e.g., a shortened duration of illness). • Persons with influenza who are already beginning to recover do not need to start treatment. <u>Postexposure Chemoprophylaxis Indications</u> • Decisions on whether to administer antivirals for chemoprophylaxis should take into account the exposed person's risk for influenza complications, the type and duration of contact, recommendations from local or public health authorities, and clinical judgment. • Postexposure chemoprophylaxis for persons should be only used when antivirals can be started within 48 hours of the most recent exposure. • Chemoprophylaxis with antiviral medications is not a substitute for influenza vaccination when influenza vaccine is available. • Either oseltamivir or zanamivir is recommended for antiviral chemoprophylaxis of 2009 H1N1, influenza A (H3N2), or influenza B influenza virus infection. • An emphasis on early treatment is an alternative to chemoprophylaxis in managing certain persons who have had a suspected exposure to influenza virus. <u>Duration of Chemoprophylaxis</u> • Postexposure chemoprophylaxis is administered for no more than 10 days after the most recent known exposure to a close contact known to have influenza. • The duration of pre-exposure chemoprophylaxis based on potential exposure in the community depends on the duration of community influenza activity. Regimens as long as 28 days for zanamivir, and 42 days for oseltamivir, have been well tolerated, but no published data are available regarding use of regimens lasting >6 weeks. <u>Control of Influenza Outbreaks in Institutions</u> • Use of antiviral drugs for treatment and chemoprophylaxis of influenza is a key component of influenza outbreak control in institutions that house patients at higher risk for influenza complications. • Both adamantanes and neuraminidase inhibitors have been used successfully to control outbreaks caused by susceptible strains when antiviral medications are combined with other infection-control measures. • When chemoprophylaxis is indicated, a neuraminidase inhibitor medication should be started as early as possible to reduce the spread of the virus. • Chemoprophylaxis should be administered to all eligible residents, regardless of whether they received influenza vaccination during the previous fall, and should continue for a minimum of 2 weeks. If surveillance indicates that new cases continue to occur,

Clinical Guideline	Recommendation(s)
	chemoprophylaxis should be continued until approximately 10 days after illness onset in the last patients. • During institutional outbreaks, chemoprophylaxis also can be offered to unvaccinated staff members who provide care to persons at high risk of complications. • Chemoprophylaxis should be considered for all employees, regardless of their influenza vaccination status, if indications exist that the outbreak is caused by a strain of influenza virus that is not well matched by the vaccine.

American Academy of Pediatrics (AAP): **Recommendations for Prevention and Control of Influenza in Children, 2011-2012**[13] **(2011)**	<u>Annual Influenza Vaccination is Recommended for the Following Groups:</u>
	• All children, including infants born prematurely, 6 months of age and older with conditions that increase the risk of complications from influenza.
	• Household contacts and out-of-home care providers of:
	  o Children with high-risk conditions
	  o Children younger than 5 years of age
	• Health care professionals
	• All women who are pregnant, considering pregnancy, or breastfeeding during the influenza season.
	<u>Use of Antiviral Medications</u>
	• Oseltamivir and zanamivir are the only antiviral medications routinely recommended for chemoprophylaxis or treatment during the 2011–2012 season.
	• All strains of influenza currently anticipated to circulate are susceptible to neuraminidase inhibitors, but have high rates of resistance to amantadine and rimantadine.
	• Treatment should be considered for:
	  o Any child hospitalized with presumed influenza or with severe, complicated, or progressive illness, regardless of influenza immunization status.
	  o Influenza infection of any severity in children at high risk of complications of influenza infection.
	  o Any otherwise healthy child with influenza infection for whom a decrease in duration of clinical symptoms is felt to be warranted by his or her provider if treatment can be initiated within 48 hours of illness onset.
	• Earlier treatment provides more optimal clinical responses, although treatment after 48 hours of symptoms in the child with moderate-to-severe disease or with progressive disease might still provide some benefit.
	• Children <1 year of age are at increased risk of influenza-related complications. Although there are no antiviral medications licensed by the Food and Drug Administration for this age group and the 2009 H1N1 pandemic Emergency Use Authorization has expired, recommendations for use of oseltamivir in this young age group can still be followed.
	• Antiviral treatment should be started as soon as possible after illness onset and should not be delayed while waiting for a definitive influenza test result.
	<u>Recommendations for Chemoprophylaxis During an Influenza Outbreak</u>
	• For children at high risk of complications from influenza for whom influenza vaccine is contraindicated.
	• For children at high risk during the 2 weeks after influenza immunization.
	• For family members or HCP who are unimmunized and are likely to

Clinical Guideline	Recommendation(s)
	have ongoing, close exposure to: unimmunized children at high risk; or infants and toddlers who are younger than 24 months. • For control of influenza outbreaks for unimmunized staff and children in a closed institutional setting with children at high risk. • As a supplement to immunization among children at high risk, including children who are immunocompromised and might not respond to vaccine. • As postexposure prophylaxis for family members and close contacts of an infected person if those people are at high risk of complications from influenza. • Chemoprophylaxis should not be considered a substitute for immunization.

Infectious Diseases Society of America (IDSA): **Seasonal Influenza in Adults and Children— Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practice Guidelines of the Infectious Diseases Society of America[12] (2009)**	<u>Antivirals for Treatment of Seasonal Influenza</u>
	• Treatment is recommended for both adults and children with influenza virus infection who meet the following criteria:
	  o Persons with laboratory-confirmed or highly suspected influenza virus infection at high risk of developing complications within 48 h after symptom onset. Treatment is recommended regardless of influenza vaccination status and regardless of severity of illness.
	  o Persons requiring hospitalization for laboratory-confirmed or highly suspected influenza illness, regardless of underlying illness or influenza vaccination status, if treatment can be initiated within 48 h after onset of symptoms. However, persons who require hospitalization for laboratory-confirmed influenza whose positive laboratory test result for influenza is from a specimen obtained >48 h after the onset of illness may also benefit from treatment.
	• Treatment should be considered for both adults and children with influenza virus infection who meet the following criteria:
	  o Outpatients at high risk of complications with illness that is not improving and who have a positive influenza test result from a specimen obtained >48 h after onset of symptoms.
	  o Outpatients with laboratory-confirmed or highly suspected influenza virus infection who are not at increased risk of complications, whose onset of symptoms is >48 h before presentation, and who wish to shorten the duration of illness and further reduce their relatively low risk of complications or who are in close contact with persons at high risk of complications secondary to influenza infection. Those whose onset of symptoms occurred >48 h before presentation with persisting moderate to severe illness may also benefit from treatment, but safety and efficacy in this population have not been evaluated prospectively.
	• On the basis of antiviral susceptibility patterns current as of March 2009, infection with an influenza A (H1N1) virus should be treated with either zanamivir or an adamantine (preferably rimantadine because of its more favorable adverse effect profile); oseltamivir should not be used to treat infection with influenza A (H1N1). Infection with an influenza A (H3N2) virus should be treated with oseltamivir or zanamivir; the adamantanes should not be used to treat influenza A (H3N2). If subtype information is unavailable, influenza A should be treated either with zanamivir or with a combination of oseltamivir and rimantadine. Infection with an influenza B virus should be treated only with oseltamivir or zanamivir.
	<u>Antivirals for Chemoprophylaxis of Seasonal Influenza</u>

Clinical Guideline	Recommendation(s)
	• Influenza vaccination is the primary tool to prevent influenza, and antiviral chemoprophylaxis is not a substitute for influenza vaccination. When influenza viruses are circulating in the community, chemoprophylaxis can be considered for high-risk persons during the 2 weeks after vaccination before an adequate immune response to inactivated vaccine develops (6 weeks for children who were not previously vaccinated and who require 2 doses of vaccine). • Antiviral chemoprophylaxis should be considered for adults and children aged ≥1 year who are at high risk of developing complications from influenza for which influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g., persons who are significantly immunocompromised). • Antiviral chemoprophylaxis (in conjunction with prompt administration of the inactivated vaccine) should be considered for adults and children aged ≥1 year who are at high risk of developing complications from influenza virus infection and have not yet received influenza vaccine when influenza activity has already been detected in the community. • Antiviral chemoprophylaxis may be considered for unvaccinated adults, including health care workers, and for children aged ≥1 year that are in close contact with persons at high risk of developing influenza complications during periods of influenza activity. Whenever possible, influenza vaccine should be administered; 2 weeks after administration, chemoprophylaxis may be discontinued. • Antiviral chemoprophylaxis is recommended for all residents (vaccinated and unvaccinated) in institutions that are experiencing influenza outbreaks. • The strongest consideration for use of antiviral chemoprophylaxis should be given to persons at the highest risk of influenza-associated complications. • Antiviral chemoprophylaxis should be considered for persons at high-risk of developing complications from influenza if influenza vaccine is not available due to shortage. If vaccine is available, it should be administered to these persons. • Antiviral chemoprophylaxis can be considered for high-risk persons in situations in which there is documented low influenza vaccine clinical effectiveness because of the circulation of influenza virus strains that are antigenically distant from the vaccine strains, such that a substantial increase in vaccine failures is anticipated, as determined by federal, state, and local public health authorities. • In persons at high risk of complications who are not adequately protected as a result of poor immune responses (e.g., in persons who are significantly immunocompromised), lack of influenza vaccination, or ineffective vaccine (e.g., when antigenically distant strains are circulating), antiviral chemoprophylaxis should be initiated at the onset of sustained community influenza activity, as determined by local public health authorities. • Antiviral chemoprophylaxis use for appropriate persons within households should be initiated when 1 family member develops suspected or confirmed influenza and any other family member is at high risk of complications secondary to infection, including infants aged <6 months. In this setting, all noninfected family members should receive antiviral chemoprophylaxis. • If inactivated influenza vaccine is administered, antiviral chemoprophylaxis can generally be stopped 2 weeks after vaccination for persons in non-institutional settings.

Clinical Guideline	Recommendation(s)
	• When antiviral chemoprophylaxis is used in a household after the diagnosis of influenza in 1 family member, chemoprophylaxis should be continued for 10 days. • In persons at high risk of developing complications from influenza for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g., persons who are significantly immunocompromised), chemoprophylaxis should continue for the duration that influenza viruses are circulating in the community during influenza season. • On the basis of antiviral susceptibility patterns current as of March 2009, either zanamivir or an adamantane (preferably rimantadine because of its more favorable adverse effect profile) should be used for influenza A (H1N1) chemoprophylaxis; oseltamivir should not be used for influenza A (H1N1) chemoprophylaxis. Either oseltamivir or zanamivir should be used for influenza A (H3N2) chemoprophylaxis; the adamantanes should not be used for influenza A (H3N2) chemoprophylaxis. If subtype information is unavailable, either zanamivir or a combination of oseltamivir and rimantadine should be used for influenza A chemoprophylaxis. Only oseltamivir or zanamivir should be used for influenza B chemoprophylaxis.
World Health Organization (WHO) Rapid Advice Guideline Panel on Avian Influenza: **WHO Rapid Advice Guidelines for Pharmacological Management of Sporadic Human Infection with Avian Influenza A (H5N1) Virus**[14] **(2007)**	• Clinicians should administer oseltamivir treatment as soon as possible in patients with confirmed or strongly suspected H5N1 infection. • Clinicians might administer zanamivir in patients with confirmed or strongly suspected infection with H5N1 virus. • Clinicians should not administer amantadine or rimantadine alone as first-line treatment to patients with confirmed or strongly suspected human infection with H5N1 if neuraminidase inhibitors are available. • Clinicians might administer amantadine or rimantadine as a first-line treatment to patients with confirmed or strongly suspected infection with H5N1 if neuraminidase inhibitors are not available and especially if the virus is known or likely to be susceptible. • Clinicians might administer a combination of a neuraminidase inhibitor and amantadine or rimantadine to patients with confirmed or strongly suspected infection with H5N1 if neuraminidase inhibitors are available and especially if the virus is known or likely to be susceptible. • Oseltamivir or zanamivir should be administered as chemoprophylaxis continuing for 7-10 days after the last known exposure in high-risk exposure groups. • Oseltamivir or zanamivir might be administered as chemoprophylaxis continuing for 7-10 days after the last known exposure in moderate-risk exposure groups. • Oseltamivir or zanamivir should probably not be administered as chemoprophylaxis in low-risk exposure groups. • Amantadine or rimantadine should not be administered as chemoprophylaxis against human infection with H5N1 if the virus is known or likely to be resistant. • Amantadine or rimantadine might be administered as chemoprophylaxis against human infection with H5N1 in high or moderate-risk exposure groups if neuraminidase inhibitors are not available and especially if the virus is known or likely to be susceptible. • Amantadine or rimantadine should probably not be administered as chemoprophylaxis against human infection with H5N1 virus in low-risk exposure groups if neuraminidase inhibitors are not available and

Clinical Guideline	Recommendation(s)
	even if the virus is known or likely to be susceptible.
American Academy of Neurology (AAN): **Neuroprotective Strategies and Alternative Therapies for Parkinson's Disease (2006)**[16]	• No treatment to date has been shown to be neuroprotective in Parkinson's disease. • There is insufficient evidence to support or refute the use of amantadine for neuroprotection in patients with Parkinson's disease. • Evidence for the use of amantadine was rated Level U, "data inadequate or conflicting; given current knowledge, treatment is unproven."
American Academy of Neurology (AAN): **Treatment of Parkinson Disease with Motor Fluctuations and Dyskinesia (2006)**[17]	• Parkinson Disease (PD) is a progressive neurodegenerative disorder with cardinal motor features of tremor, bradykinesia, and rigidity. • Although initially effective, dopaminergic therapies are eventually complicated by motor fluctuations, including off time (periods of return of PD symptoms when medication effect wears off) and dyskinesia (drug-induced involuntary movements including chorea and dystonia) in most patients. • Amantadine is possibly effective in reducing dyskinesia. • Amantadine may be considered for patients with Parkinson's disease with motor fluctuations in reducing dyskinesia. • Evidence for the use of amantadine was rated Level C, "possibly effective, ineffective or harmful for the given condition in the specified population."

III. Indications

The Food and Drug Administration (FDA)-approved indications for the adamantanes are noted in Table 3. 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 3. FDA-Approved Indications for the Adamantanes[1-3]

Indication	Amantadine	Rimantadine
Prophylaxis of influenza virus type A	✔	✔
Treatment of influenza virus type A	✔	✔
Treatment of parkinsonism	✔	
Treatment of drug-induced extrapyramidal reactions	✔	

IV. Pharmacokinetics

The pharmacokinetic parameters of the adamantanes are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Adamantanes[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Amantadine	86-94	59-67	Not reported	Renal	17
Rimantadine	117	40	Liver	Renal (74)	25-32

V. Drug Interactions

Significant drug interactions with the adamantanes are listed in Table 5.

Table 5. Significant Drug Interactions with the Adamantanes[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Adamantanes	2	Influenza virus vaccine	Adamantanes may inhibit the replication of live vaccine virus thereby decreasing the production of influenza strain-specific antibodies.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the adamantanes are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Adamantanes[1-3]

Adverse Events	Amantadine	Rimantadine
Cardiovascular		
Arrhythmia	<1	-
Cardiac arrest	<1	-
Cardiac failure	-	<1
Heart block	-	<1
Heart failure	<1	-
Hypertension	-	<1
Orthostatic hypotension	1-10	-
Palpitation	-	<1
Peripheral edema	1-10	<1
Syncope	-	<1
Tachycardia	-	<1
Central Nervous System		
Aggressive behavior	<1	-
Agitation	1-10	<1
Amnesia	<1	-
Anxiety	1-10	-
Ataxia	1-10	<1
Coma	<1	-
Concentration impaired	-	≤2
Confusion	1-10	<1
Delirium	1-10	-
Delusions	<1	-
Depression	1-10	<1
Dizziness	1-10	1-2
Dream abnormality	1-10	-
Euphoria	<1	<1
Fatigue	1-10	1
Gait abnormality	-	<1
Hallucinations	1-10	<1
Headache	1-10	1
Insomnia	1-10	2-3
Irritability	1-10	-
Lightheadedness	1-10	-

Adverse Events	Amantadine	Rimantadine
Mania	<1	-
Nervousness	1-10	1-2
Paresthesia	<1	-
Psychosis	<1	-
Seizure	<1	<1
Somnolence	1-10	-
Suicidal ideation	<1	-
Suicide	<1	-
Tremor	-	<1
Dermatologic		
Eczematoid dermatitis	<1	-
Livedo reticularis	1-10	-
Photosensitivity	<1	-
Rash	<1	<1
Gastrointestinal		
Abdominal pain	-	1
Anorexia	1-10	2
Constipation	1-10	-
Diarrhea	1-10	<1
Dysphagia	<1	-
Nausea	1-10	3
Taste alteration	-	<1
Vomiting	-	2
Xerostomia	1-10	2
Hematologic		
Agranulocytosis	<1	-
Leukopenia	<1	-
Neutropenia	<1	-
Laboratory Test Abnormalities		
Alkaline phosphatase increased	<1	-
ALT increased	<1	-
AST increased	<1	-
Bilirubin increased	<1	-
BUN increased	<1	-
CPK increased	<1	-
GGT increased	<1	-
LDH increased	<1	-
Serum creatinine increased	<1	-
Respiratory		
Bronchospasm	-	<1
Dry nose	1-10	-
Dyspnea	<1	<1
Pulmonary edema	<1	-
Respiratory failure	<1	-
Other		
Allergic reaction	<1	-
Anaphylaxis	<1	-
Diaphoresis	<1	-
Hyperkinesia	<1	<1
Lactation	-	<1
Neuroleptic malignant syndrome	<1	-
Oculogyric episodes	<1	-
Urinary retention	<1	-
Withdrawal reactions	<1	-

Adverse Events	Amantadine	Rimantadine
Visual disturbances	<1	-
Weakness	-	1

✓ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the adamantanes are listed in Table 7.

Table 7. Usual Dosing Regimens for the Adamantanes[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amantadine	Drug-Induced Extrapyramidal Reactions: 100 mg twice daily Parkinsonism: Monotherapy: 100 mg twice daily Concomitant therapy: 100 mg once or twice daily Prophylaxis and Treatment of Influenza A Virus Illness: 200 mg as a single daily dose or 100 mg twice daily	Prophylaxis and Treatment of Influenza A Virus Illness: 1-9 years of age: 4.4 to 8.8 mg/kg/day divided twice daily 9-12 years of age: 100 mg twice daily	Capsule: 100 mg Syrup: 50 mg/5 ml Tablet: 100 mg
Rimantadine	Prophylaxis and Treatment of Influenza A Virus Illness: 100 mg twice daily	Prophylaxis of Influenza A Virus Illness: <10 years of age: 5 mg/kg once daily ≥10 years of age: 100 mg twice daily	Tablet: 100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the adamantanes are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Adamantanes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Influenza Prophylaxis				
Bryson et al.[21] (1980) Amantadine for 4 weeks vs placebo	DB, PRO, RCT, XO Young adults attending college	N=88 4 weeks	Primary: Gross and subtle side effects	Primary: Adverse events occurred in 33% of those receiving amantadine and in 10% of those receiving placebo (P<0.005). Cessation of adverse events occurred in more than half of those continuing amantadine. Sixteen students receiving amantadine had decreased performance on sustained attention tasks as compared with ones receiving placebo (P<0.05).
Dolin et al.[22] (1982) Amantadine 100 mg BID for 6 weeks vs rimantadine 100 mg BID for 6 weeks vs placebo	DB, PC, RC Healthy non-vaccinated adults aged 18 to 45 who volunteered for the study	N=450 6 weeks	Primary: Efficacy, defined as number of influenza-like illnesses, and number of laboratory-confirmed influenza cases Secondary: Adverse events	Primary: Influenza-like illness occurred in 41% of the patients receiving placebo, 14% of those receiving rimantadine, and 9% of those receiving amantadine (P<0.001 for either drug vs placebo). Laboratory-documented influenza occurred in 21% of placebo recipients, 3% of rimantadine recipients, and 2% of amantadine recipients (P<0.001 for either drug vs placebo). These findings represent efficacy rates of 85% for rimantadine and 91% for amantadine, as compared with placebo. Secondary: More recipients of amantadine (13%) than recipients of rimantadine (6%; P<0.05) or placebo (4%; P<0.01) withdrew from the study because of central nervous system side effects.
Reuman et al.[23] (1989) <u>Study 1 (naturally occurring influenza):</u>	DB, PC, RCT Healthy hospital personnel aged 18 to 55 years	<u>Study 1:</u> N=476 6 weeks <u>Study 2:</u> N=78	Primary: Efficacy, as measured by number of influenza-like illnesses, number	Primary: In the first study, adverse reactions were not significantly different between the group receiving 100 mg/day of amantadine and the placebo group, but significantly greater in the group given 200 mg/day (P<0.009). The study authors concluded that the influenza attack rate in this study

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amantadine 100 mg QD vs amantadine 200 mg QD vs placebo <u>Study 2 (experimental challenge):</u> Amantadine 50 mg QD vs amantadine 100 mg QD vs amantadine 200 mg QD		13 days	of laboratory-confirmed influenza cases using blood tests and viral assays from nasal washouts	was too low to assess efficacy. In the experimental challenge study of influenza A/Beth/1/85, the prophylactic administration of amantadine 50 mg, 100 mg or 200 mg/day doses was more effective than placebo in preventing influenza illness (P<0.02, 66%, 74% and 82% protection, respectively), and in suppressing viral replication (P=0.02). There was no significant difference between amantadine groups in influenza illness or viral shedding. Compared with the placebo group the 100 mg and 200 mg amantadine groups showed a significant decrease in infection rate (100 mg: 40% protection: P=0.012; 200 mg: 32% protection: P=0.045) whereas the 50 mg group did not (20% protection: P=0.187).
Brady et al.[24] (1990) Rimantadine 100 mg QD vs placebo	DB, MC, PC Healthy adult volunteers aged 18 to 55 years	N=228 3 months	Primary: Prophylactic efficacy, as judged from laboratory-confirmed influenza virus infections and number of illnesses from influenza A	Primary: Compared with placebo, low-dose rimantadine was associated with significantly fewer cases of influenza A virus infection (20 of 110 in the placebo group vs 7 of 112 in the rimantadine group; P<0.01) and influenza illness (7 of 110 in the placebo group vs 1 of 112 in the rimantadine group; P=0.04). Secondary: Only 10 (8.7%) of 114 rimantadine recipients and 5 (4.4%) of 114 placebo control recipients reported one or more mild-to-moderate adverse

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Adverse effects	symptoms, most of which were related to the gastrointestinal or central nervous system.
Crawford et al.[25] (1988) Rimantadine vs placebo	DB, PC, RCT Children ages 1 to 18 years and adult members from 29 families	N=110 A naturally occurring outbreak of influenza A (H3N2)	Primary: Efficacy against influenza A infection and associated illness, prevention of transmission of infection to adult members of the child's family, and adverse effects	Primary: Influenza infections, defined as a positive viral throat culture or a 4-fold increase in antibody titer, occurred in 31% of children in the placebo group and 7.4% in the rimantadine group (P=0.026). Clinical illness with laboratory evidence of influenza infection occurred in 24.1% of children in the placebo group and none in the rimantadine group (P=0.007). Rimantadine was well-tolerated by the children, with no significant differences in adverse events between the treatment groups.
Hayden et al.[26] (1989) Rimantadine 200 mg QD for 10 days vs placebo	DB, PC, RCT Household members of patients with influenza A	N=237 (families) Two influenza seasons	Primary: Development of illness and resistance	Primary: Among households with documented influenza A infections, symptomatic illness occurred in one or more contacts in 10 of 28 families treated with rimantadine and in 10 of 209 families treated with placebo. Asymptomatic secondary influenza A infections were found in five families assigned to receive rimantadine and in four families assigned to receive placebo. Rimantadine-resistant strains of influenza A virus (H3N2 subtype) with mutations consisting of single amino acid changes in the M2 protein (residue 27, 30, or 31) were recovered from eight index patients and five contacts treated with rimantadine. There was apparent transmission of drug-resistant strains of virus in six contacts with secondary illnesses in five families.
Monto et al.[27] (1995) Rimantadine 100 mg QD up to 8 weeks vs	DB, PC, RCT Elderly residents in 10 nursing homes	N=328 8 weeks	Primary: Incidence of adverse effects Secondary: Influenza like illness; laboratory-confirmed clinical influenza;	Primary: The most commonly reported symptom in all groups was confusion (10% to 14%). Nausea (8% to 11%) and loss of appetite (6% to 10%) were also frequently reported. Four (3%) patients in the 200 mg/day group and one (2%) participant in the placebo group experienced a seizure or clonic twitching while receiving study drug or placebo. Patients in all 3 groups were equally likely to experience each of the specified symptoms. Patients in the 200 mg/day-prophylaxis group were 2.3 times more likely

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rimantadine 200 mg QD up to 8 weeks vs placebo			influenza virus infection with or without clinical illness	to experience a significant health event than those in the placebo group (P=0.031). Patients in the 200 mg/day group were 1.9 times more likely to withdraw from the study than patients in the placebo group. A total of 31/132 patients withdrew from the 200 mg group (P=0.041). Increased risk of withdrawal from the study was also observed when comparing the 100 mg/day group with the placebo group. A total of 23/130 patients withdrew from the 100 mg group (P=0.213). Secondary: Rimantadine at both dosages was associated with reductions in the likelihood of clinical influenza-like illness and laboratory-confirmed influenza virus infection; however, in no case were the estimates statistically significant. Efficacy analyses were limited to vaccinated individuals. Efficacy analyses to be carried out in 2 of the 10 nursing homes where study patients had documented influenza virus infection. Rimantadine was most efficacious at reducing the likelihood of clinical illness; the relative risk (RR) was 0.40 (95% CI: 0.13 to 1.25, P=0.115) and 0.43 (95% CI: 0.14 to 1.35; P=0.147) for 100 mg and 200 mg doses respectively. However, rimantadine was less effective in reducing the likelihood of laboratory-confirmed infection; the RR were 0.50 (95% CI: 0.12 to 2.18; P=0.355) and 0.54 (95% CI: 0.12 to 2.34; P=0.409) for 100 mg and 200 mg doses, respectively. The efficacy of rimantadine in reducing the likelihood of clinical influenza-like illness was estimated to be 58% (RR=0.42, CI: 0.16 to 1.11, P=0.079) for the groups receiving prophylaxis vs placebo.
Jefferson et al.[28] (2006) Amantadine, rimantadine, or neuraminidase inhibitors (NI) as	MA Healthy individuals aged 16-65	52 trials Variable duration	Primary: Prophylactic efficacy, duration of nasal shedding, time to alleviate symptoms, adverse events, lower	Primary: For the prophylaxis of influenza A and influenza-like illness, amantadine prevented 61% (95% CI: 35 to 76) and 25% (95% CI: 13 to 36) of cases respectively. The use of amantadine was associated with nausea (OR 2.56, 95% CI: 1.37 to 4.79), insomnia and hallucinations (2.54, 95% CI: 1.50 to 4.31).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
prophylaxis and/or treatment for influenza vs placebo, no intervention, or symptomatic medication			respiratory tract complications	The duration of fever in days was significantly shortened with amantadine compared to placebo (0.99, 95% CI: –1.26 to -0.71); in comparison with nasal shedding of influenza A, there were no significant difference was seen (0.93, 95% CI: 0.71 to 1.21). Compared with placebo when used for prophylaxis, NI have no significant effect on influenza-like illness (1.28, 95% CI: 0.45 to 3.66 for oseltamivir 75 mg a day and 1.51, 95% CI: 0.77 to 2.95 for zanamivir 10 mg a day). Against symptomatic influenza, oseltamivir was 61% or 73% (75 mg and 150 mg doses) effective, while zanamivir was 62% efficacious. Nausea was associated with the use of oseltamivir (OR 1.79, 95% CI: 1.10 to 2.93). The protective efficacy of oseltamivir was 58.8% from household contacts and from 68% to 89% in contacts of index cases. Compared to placebo the HRs for the time-to-alleviate symptoms were 1.33 (95% CI: 1.29 to 1.37) for zanamivir and 1.30 (95% CI: 1.13 to 1.50) for oseltamivir, when the medications were started within 48 hours of onset of symptoms. In preventing lower respiratory tract complications in influenza cases, oseltamivir 150 mg a day was judged to be effective (OR 0.32, 95% CI: 0.18 to 0.57).
Kimberlin et al.[8] (2010) Amantadine vs rimantadine vs	RETRO Children <12 months of age with influenza	N=180 Variable duration	Primary: Frequency of neurologic adverse events and all adverse events	Primary: Abnormalities that potentially reflected neurologic involvement were consistent with influenza disease, related to preexisting underlying neurologic conditions, or explainable by a concomitant medication. Two patients had possible seizures or seizure-like movements during therapy with no preexisting history of such events, but in both cases the seizures were not thought to be related to antiviral therapy. Only 33% of the patients had Glasgow Coma Score (GCS) information available in their medical records. The end-of-treatment ranked verbal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oseltamivir				score was slightly lower for oseltamivir treated patients (P=0.04). Total scores were identical between the 2 therapies (P=0.40). One death occurred within 30 days following initiation of the influenza antiviral medications.
Jackson et al.[7] (2011) Amantadine vs oseltamivir vs zanamivir vs	MA Patients who received antiviral agents for the prevention of influenza	20 trials Variable duration	Primary: Prevention of symptomatic laboratory-confirmed influenza (SLCI) Secondary: Complications prevented, hospitalizations prevented, length of influenza illness and time to return to normal activities	Primary: Oseltamivir was efficacious in seasonal prophylaxis against (RR 0.24; 95% CI, 0.09-0.54). A protective effect of oseltamivir in seasonal prophylaxis was found in one study which included the frail elderly living in residential care (RR 0.08; 95% CI, 0.01-0.63). Oseltamivir was effective in preventing the transmission of SLCI in households of mixed composition (RR 0.19; 95% CI 0.08-0.45). Oseltamivir have a preventative effect against SLCI when employed as post-exposure prophylaxis in pediatric contacts (≥1 year of age; (RR 0.36; 95% CI, 0.15-0.84). Zanamivir demonstrated a protective efficacy of 68% for seasonal prophylaxis in adults (RR 0.32; 95% CI 0.17-0.63) and at-risk adolescents/adults (RR 0.17; 95% CI, 0.07-0.44). There was no significant different in older people with zanamivir. Zanamivir was effective in preventing the transmission of SLCI in households of mixed composition (RR 0.21; 95% CI, 0.13-0.33). There was no significant difference in the elderly in long-term care (RR 0.68; 95% CI 0.33-1.27). Evidence for the use of amantadine against SLCI in seasonal prophylaxis was limited. One trial demonstrated a non-significant preventative effect among healthy adults in seasonal prophylaxis (RR 0.40; 95% CI 0.08-2.03). Amantadine was effective in preventing SLCI in healthy adolescents (RR 0.10;95% CI 0.03-0.34). Secondary: Oseltamivir seasonal prophylaxis was associated with a non-significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				78% reduction in secondary complications among at-risk elderly patients with laboratory-confirmed influenza (P=1.14). In a study of post-exposure prophylaxis, the proportion of contacts with laboratory-confirmed influenza with at least one secondary complication was equivalent among patients who received oseltamivir and those in the control arm who received expectant treatment upon the onset of influenza-like illness (7% versus 5%). However, the more severe respiratory complications occurred among the expectant treatment group. The median duration of illness in contacts was shorter in the oseltamivir post-exposure prophylaxis group versus those receiving treatment on influenza onset (5.5 hours versus 39.8 hours; P=0.103). Fewer contacts with laboratory-confirmed influenza in the oseltamivir post-exposure prophylaxis group were bedbound compared with patients in those receiving treatment on influenza onset (7% versus 28%). Significantly less work absence was reported among patients who received zanamivir as seasonal prophylaxis versus control group patients (mean hours lost 0.6 vs 1.4; P=0.001). Total productive time lost was also less in the zanamivir group (1.8 vs 3.0 hours; P=0.001). Significantly fewer households who received zanamivir post-exposure prophylaxis reported a contact developing a complication of laboratory-confirmed influenza (2% vs 6%;P=0.01). Complications of SLCI during the first 28 days following postexposure prophylaxis initiation were lower among the zanamivir-treated patients versus placebo (5% vs 6%; P=0.653). The proportion of cases with complications requiring antibiotics was marginally lower among patients receiving zanamivir post-exposure prophylaxis compared with placebo (5% vs 8%). Among household contacts with laboratory-confirmed influenza, the median time to alleviation of symptoms without use of medication was 5.5 days in the prophylaxis and 8.0 days in the placebo groups. Mean duration of significant influenza-like symptoms was shorter in the zanamivir post-exposure prophylaxis versus placebo group (0.2 vs 0.6 days; P=0.016). No secondary outcomes were described relating to the use of amantadine in seasonal prophylaxis.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Limited evidence was identified for milder influenza illness of shorter duration as a result of the use of amantadine in post-exposure prophylaxis. The severity of symptoms was reported as 56.0% mild and 9.0% severe in the amantadine group, and 38.0% mild and 19.0% severe in the placebo group (P<0.01 for severe symptoms, P<0.001 for mild symptoms). Mean duration of illness was found to be shorter in the amantadine group versus the placebo group (P<0.05).
Influenza Treatment				
Younkin et al.[29] (1983) Amantadine 100 mg orally QD for 5 days vs amantadine 200 mg orally QD for 5 days vs aspirin 3.25 g orally QD for 5 days	DB, PRO College students, ages 17 to 20 years, with symptoms of less than 48 hours duration	N=48 7 days	Primary: Symptomatic improvement; symptoms measured included upper respiratory symptoms (earache or obstruction, nasal discharge or obstruction, sore throat, hoarseness), lower respiratory symptoms (chest pain, cough), and systemic symptoms (feverishness, chills, myalgias, malaise, headache, and anorexia). Secondary: Side effects	Primary: The aspirin treatment group defervesced more rapidly, in 10.3 hours vs 21.5 hours for the amantadine 100 mg group and 23.6 hours for the amantadine 200 mg group (P<0.01). When mean daily symptom scores were tabulated, the volunteers receiving 100 mg of amantadine daily had significantly lower values at 48 hours and 72 hours than did the volunteers receiving aspirin (P<0.01). Although the group who received 200 mg of amantadine had substantially lower overall symptom scores than the aspirin treatment group, this difference did not achieve statistical significance (0.05<P<0.01). Secondary: Bothersome side effects resulted in discontinuation of therapy by 35% of patients in the aspirin group but only 3% of patients in the amantadine treatment group (P<0.05).
Hall et al.[30] (1987) Rimantadine 6.6 mg/kg/day up to 150 mg/day for	DB, RCT Children 1 to 15 years of age with influenza-like illness	N=69 7 days	Primary: Reduction in fever, improvement in daily scores for symptoms, severity of illness, and viral	Primary: Children receiving rimantadine showed significantly greater reduction in fever and improvement in daily scores for symptoms and severity of illness during the first three days (P<0.04). Viral shedding also diminished significantly during the first two days but

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
children ≤9 years; 200 mg/day for children >9 years for 5 days vs acetaminophen 10 mg/kg/dose up to 500 mg/dose for 5 days			shedding	subsequently increased such that by days 6 and 7 the proportion of children shedding virus, as well as the quantity of virus shed, was significantly greater in the rimantadine group (P<0.04). During the seven-day study, of the 22 children in the rimantadine group with serial isolates tested, ten (45.5%) had resistant isolates compared with two (12.5%) of those with serial isolates in the acetaminophen group (P<0.03). Thus, of the total 37 children in the rimantadine group, 27% were found to have resistant isolates compared with 6% in the total group receiving acetaminophen (P<0.04). Furthermore, the mean inhibitory concentration of rimantadine increased with time in the rimantadine group (P=0.002) but not in the acetaminophen group.
Hayden et al.[31] (1986) Rimantadine 200 mg PO QD for 5 days vs placebo	DB, PC, RCT Patients with uncomplicated influenza A (H3N2) virus infection	N=14 2 months	Primary: Therapeutic activity	Primary: Rimantadine treatment was associated with significant reductions in nasal secretion viral titers (days 2 through 4; P<0.01), maximal temperature (days 2 and 3; P<0.01), and systemic symptoms compared with placebo treatment (P<0.01).
Kawai et al.[32] (2005) Amantadine 50 mg for adults and 1.5-2.5 mg/kg for children was administered twice daily for 5 days to patients with influenza A (Group 3) vs oseltamivir 75 mg	OL Patients diagnosed with influenza who received oseltamivir or amantadine therapy within 48 hours after symptom onset	N=2,163 5 days	Primary: Time from onset of symptoms to start of treatment, duration of fever, impact of age on outcome	Primary: For all 3 groups the duration of fever was significantly shorter in patients who received the medication within 12 hours after the onset of symptoms compared to greater than 12 hours after the honest of symptoms (P<0.001). For patients in Group 2 the duration of fever was significantly longer when compared to Groups 1 and 3, however there was no significant differences between groups 1 and 3 (P<0.01 to <0.05). The duration of fever was significantly longer for patients in Groups 2 and 3 aged 0-6 years when compared to those aged 7-15 and 16-64; P<0.001 to 0.01). The duration of fever of patients 0-6 in Group 1 was significantly shorter than for those same aged patients in Group 2 (P<0.01). For patients aged 16-64 and >65 there was no significant difference found

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for adults and 2 mg/kg for children (<37.5 kg) given twice a day for 5 days to patients with either influenza A (Group 1) or influenza B (Group 2)				between groups in duration of fever (P=NS).
Jefferson et al.[33] (2006) Oral or inhaled amantadine or oral rimantadine as prophylaxis and/or treatment for influenza vs placebo, standard medications (aspirin and other antipyretic or antiinflammatory medications), other antiviral medications, or no intervention	MA Healthy individuals aged 14 to 60	36 trials Variable duration	Primary: Numbers of influenza cases, severity of cases, rate of death, length of nasal shedding, persistence of virus in the upper airways, adverse effects	Primary: For the comparison of prophylaxis of influenza and influenza-like illness (ILI), amantadine prevented 61% (95% CI: 35 to 76) and 25% (95% CI: 13 to 36) of the cases respectively. The duration of fever was significantly shortened by amantadine compared to placebo (0.99 days; 95% CI: 0.71 to 1.26). However, there was no effect on nasal shedding of influenza A viruses in the upper airways after up to five days of treatment (RR 0.96; 95% CI: 0.72 to 1.27). Amantadine use was associated with gastrointestinal symptoms (OR 2.56; 95% CI: 1.37 to 4.79), insomnia and hallucinations (OR 2.54; 95% CI: 1.50 to 4.31), and withdrawals from the trials because of adverse events (OR 2.54; 95% CI: 1.60 to 4.06) in the prophylaxis trials. There was no evidence that amantadine use was associated with increased adverse effect rates compared to placebo use in treatment trials. For the prophylaxis of influenza and ILI, rimantadine was not effective against either influenza (RR 0.28; 95% CI: 0.08 to 1.08) or influenza-like-illness (RR 0.65; 95% CI: 0.35 to 1.20). The duration of fever was significantly shortened by rimantadine compared to placebo (1.24 days; 95% CI: -0.76 to -1.71). However, there was no effect on nasal shedding of influenza A viruses in the upper airways after up to five days of treatment (RR 0.67; 95% CI: 0.22 to 2.07). Rimantadine use was associated with experiencing all adverse effects

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				more than placebo recipients (OR 1.96; 95% CI: 1.19 to 3.22). In the comparison of amantadine vs rimantadine for prophylaxis of influenza or ILI, there was no difference in efficacy (RR 0.88, 95% CI: 0.57 to 1.35). There was no difference in efficacy comparing amantadine compared to rimantadine for treatment. The comparison of amantadine with rimantadine confirmed that central nervous system (CNS) adverse effects (OR 3.11; 95% CI: 1.67 to 5.78) and withdrawal from trials (OR 2.49; 95% CI: 1.26 to 4.93) were significantly more frequent among amantadine recipients. The effects of oral or inhaled amantadine on the shedding of influenza A viruses were not significant (RR 0.93; 95% CI: 0.71 to 1.21). There was no difference in the duration of fever in the comparison of amantadine against standard medications (weighted mean difference 0.25; 95% CI: - 0.37 to 0.87). In the comparison of inhaled amantadine vs placebo, amantadine was no more effective than placebo in bringing down the respiratory or constitutional symptom score (weighted mean difference 1.0; 95% CI: 3.64 to 1.64 and -2.0; 95% CI: 16.9 to 12.9 respectively).
Alves Galvão et al.[19] (2008) Amantadine (AMT) and rimantadine (RMT) vs placebo, control drugs, or no intervention	MA Studies evaluating the prevention and treatment of influenza with amantadine and/or rimantadine in children (<19 years of age) and the elderly (≥65 years of age)	12 trials Variable duration	Primary: Response to treatment, cases of influenza, adverse events	Primary: <u>AMT and RMT compared to control (placebo and acetaminophen) in the treatment of influenza A in children</u> There was a protective effect of AMT and RMT in the occurrence of fever on day three of antiviral treatment, when trials using both antivirals were combined (RR 0.39; 95% CI 0.20 to 0.79). The number of children needed to treat to benefit (NNTB) to prevent one case of fever on day three of treatment was 5.88 (95% CI 4.55 to 16.67). A protective effect of RMT for this outcome was also demonstrated (RR 0.36; 95% CI 0.14 to 0.91). The NNTB to prevent one case of fever on day three of treatment was 4.12 (95% CI 3.03 to 33.33). No protective effect of AMT was observed in the occurrence of fever on day three of treatment (RR 0.37; 95% CI 0.08 to 1.75).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No protective effect of RMT was seen regarding the occurrence of any of the following outcomes assessed: cases of pain on movement and visual distortion on day five (RR 0.58; 95% CI 0.10 to 3.24), conjunctivitis on day five (RR0.17; 95% CI: 0.01 to 3.49), malaise on day six (RR 1.04; 95% CI 0.63 to 1.70), and cough on day seven (RR 0.83; 95% CI 0.63 to 1.10). <u>AMT and RMT compared to control (placebo and to specific treatment) in the prophylaxis of influenza A in children</u> A protective effect of AMT was observed (RR 0.11; 95% CI 0.04 to 0.30). The NNTB was 11.1 (95% CI 10 to 14.29) for a period ranging from 14 to 18 weeks. No protective effect of RMT was seen in the prophylaxis of cases of influenza (RR 0.49; 95% CI 0.21 to 1.15). <u>Adverse effects of AMT and RMT compared to control (placebo and acetaminophen) in children</u> AMT was not related to a higher risk of the following adverse effects: diarrhea (RR 0.79; 95% CI: 0.42 to 1.47), exanthema (RR 0.69; 95% CI 0.21 to 2.34), muscular limb pain (RR 0.85, 95% CI 0.46 to 1.59), headache (RR 0.73; 95% CI 0.52 to 1.03), and stimulation and insomnia (RR 0.46; 95% CI: 0.12 to 1.74). RMT was not related to a higher risk of any of the following adverse effects assessed: CNS symptoms (RR 0.23; 95% CI 0.01 to 4.70); change in behavior (RR 0.23; 95% CI 0.01 to 4.70); diarrhea (RR 0.36; 95% CI 0.02 to 8.41); dizziness (RR 3.21; 95% CI 0.14 to 75.68); GI manifestations (RR 1.17; 95% CI 0.08 to 18.05); hyperactivity (RR 0.36; 95% CI 0.02 to 8.41); tinnitus (RR 3.21; 95% CI 0.14 to 75.68); and cerebellar ataxia (RR 2.61; 95% CI 0.11 to 61.80) <u>RMT compared to control (placebo and zanamivir) in the prophylaxis of influenza A in the elderly</u> No protective effect of RMT was seen regarding the prophylaxis of influenza in the elderly (RR 0.74; 95% CI 0.13 to 4.07). <u>Adverse effects of RMT compared to control (placebo) in the elderly</u> No effect of RMT was seen regarding any of the adverse outcomes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				assessed in the combined studies: stimulation and insomnia (RR 1.61; 95% CI 0.43 to 6.02), confusion (RR 0.79; 95% CI 95% 0.40 to 1.56), fatigue (RR 0.81; 95% CI 0.41 to 1.60) and vomiting (RR 0.99, 95% CI 0.38 to 2.60). <u>Use of different doses of AMT and RMT for prophylaxis and treatment of influenza A in the elderly</u> A reduced RMT dose of 100 mg/day was comparable to the full dose of 200 mg daily for prophylaxis of influenza in the elderly (RR 0.93; 95% CI 0.21 to 4.20). <u>Adverse effects related to different doses of RMT in the elderly</u> There was no protective effect of a reduced dose of RMT in the occurrence of the following adverse reactions in the elderly: confusion (RR 0.83; 95% CI 0.41 to 1.65), depression (RR 0.44; 95% CI 0.12 to 1.65), impaired concentration (RR 0.68; 95% CI 0.11 to 3.98), insomnia or sleeplessness (RR 1.02; 95% CI 0.26 to 3.97), loss of appetite (RR 0.62; 95% CI 0.27 to 1.46), rash or allergic reaction (RR 0.34; 95% CI 0.04 to 3.21), seizures or clonic twitching (RR 0.11; 95% CI 0.01 to 2.07), dry mouth (RR 1.16; 95% CI 0.43 to 3.11), fatigue or drowsiness (RR 1.14; 95% CI 0.45 to 2.87), headache (RR 1.02; 95% CI 0.30 to 3.42), and body weakness or debility (RR 0.91; 95% CI: 0.38 to 2.18).
Parkinson's Disease				
Sawada et al.[4] (2010) Observation period (2–3 weeks), amantadine treatment period (27 days), washout period (15 days), and placebo treatment period (27 days; Arm 1) vs	MC, PC, DB, RCT, XO Patients 20–75 years of age with Parkinson's disease	N=35	Primary: Changes in the Rush Dyskinesia Rating Scale (RDRS) Secondary: Changes in the Unified Parkinson's Disease Rating Scale-III (UPDRS-III) for motor functions, UPDRS-	Primary: Following amantadine treatment, RDRS scores improved in 64% of patients, and placebo treatment resulted in improvement in 16% of patients (P=0.016), although the period effect was not statistically significant (P=0.31). Secondary: UPDRS-IVa scores improved by 1.83 following amantadine treatment and 0.03 following placebo (P<0.001). UPDRS-IVb and III scores remained unchanged following amantadine or placebo treatment (UPDRS-IVb: P=0.87, and UPDRS-III: P=0.26). The most common adverse effect was visual hallucinations, which was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
observation period, placebo period, a washout period, and an amantadine treatment period (Arm 2) Amantadine was increased in a stepwise manner.			IVa for dyskinesia and UPDRS-IVb for motor fluctuations	observed in three patients during the amantadine treatment period. The prevalence of adverse effects was significantly greater in patients receiving amantadine treatment compared with placebo treatment (P=0.048).
Crosby et al.[34] (2003) Amantadine monotherapy or adjuvant therapy for idiopathic Parkinson's disease vs placebo	MA Patients of all ages with a clinical diagnosis of idiopathic Parkinson's disease	N=215 (6 trials) Variable duration	Primary: Parkinson's disease motor impairment rating scales, tests of motor impairments	Primary: Four of the six studies were not eligible for efficacy analysis. Three trials were crossover trails that did not present data from the first arm. One of those three trials also only presented data from the amantadine arm. The 4th trail compromised randomization and did not analyze the results on an intention to treat basis. Of the remaining two studies, one study found that amantadine treated patients were 15.0 points better in Parkinsonian symptoms severity scale after 9 weeks of treatment (average baseline score of 21.4). The study also found that patients treated with amantadine scored 28.1 points better (average baseline score of 38.3) on the activity impairment scale compared to placebo. The remaining study did not provide standard deviations or baseline scores so the study was unable to be analyzed.
Drug-Induced Extrapyramidal Reactions				
Del Dotto et al.[35] (2001) Amantadine 200 mg IV over 2 hours vs placebo	DB, PC, RCT, XO Patients with Parkinson's disease with levodopa-induced dyskinesias, and not previously exposed to amantadine; order in which the drugs were	N=9 77 hours	Primary: Average dyskinesia score as determined by a version of the Abnormal Involuntary Movement Scale (AIMS) modified to quantify dyskinesias in the	Primary: The average dyskinesia score was lower on the days amantadine was taken compared to placebo days (4.1 ± 1.7 and 8.3 ± 1.8, respectively; P<0.01). Dyskinesia ratings from videotapes was lower on the days amantadine was taken compared to placebo days (3.5 ± 1.1 and 7.3 ± 1.6, respectively, P<0.01). The order of drug administration (amantadine-placebo vs placebo-amantadine) was apparent to 7 of the 9 patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2 infusion sessions were completed at either a 48- or 72-hour time interval. Patients received either drug or placebo after their first morning dose of levodopa.	administered (crossover study) was determined by random assignment		face, neck, trunk, and limbs Secondary: Parkinsonian symptoms	Secondary: There were no differences in parkinsonian symptoms as quantified by the average tapping and Unified Parkinson's Disease Rating Scale (UPDRS)-III scores on days when patients received amantadine vs days on placebo.
Metman et al.[36] (1998) Amantadine 100 mg for 3 weeks vs placebo	DB, PC, XO Patients with advanced Parkinson's disease complicated by motor fluctuations and peak-levodopa-dose (also known as "on") dyskinesia. Mean age was 60 years and mean symptom duration was 13 years.	N=18 3 weeks	Primary: Parkinsonian symptoms and choreiform dyskinesias as observed during the last 2 hours of a 7-hour levodopa infusion, symptoms were scored using an abbreviated Unified Parkinson's Disease Rating Scale (UPDRS) and a modified Abnormal Involuntary Movement Scale (AIMS). Secondary: Dyskinesias scored by a neurologist who observed the patients via study videotapes	Primary: In the 14 patients completing this trial, amantadine reduced dyskinesia severity by 60% compared to placebo (P=0.001), without altering the antiparkinsonian effect of levodopa. Motor fluctuations occurring with patients' regular oral levodopa regimen also improved according to UPDRS and patient-kept diaries. Parkinsonian symptoms measured during the levodopa infusion were similar with the addition of amantadine to the symptoms observed with placebo. Although 4 patients had to discontinue because of adverse effects from active treatment, including confusion, hallucinations, palpitations, and nausea, all 14 patients completing the study requested that amantadine be added to their usual antiparkinsonian regimen. Secondary: Dyskinesia ratings from videotapes scored by a second masked rater decreased by 49% with amantadine (3.6 ± 0.6) compared with placebo (7.0 ± 0.9; P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metman et al.[37] (1999) Amantadine 100 mg 3 or 4 times a day vs placebo All other antiparkinsonian medications were continued until the night before levodopa infusion was administered.	DB, PC Patients from the above study on the effects of amantadine on levodopa-induced motor complications, evaluated 1 year later.	N=17 1 year + 7-10 days of supervised administration	Primary: Parkinsonian symptoms and dyskinesia severity evaluated after a 7-hour levodopa infusion, symptoms were scored using standard rating scales and compared to results from 1 year earlier. Secondary: Dyskinesias scored by a neurologist via watching a videotape	Primary: One year after initiation of amantadine cotherapy, its antidyskinetic effect was similar in magnitude (56% reduction in dyskinesia, P<0.01, as compared to the placebo arm of the preceding trial. The reduction with amantadine one year earlier had been 60%). Motor complications occurring with the patients' regular oral levodopa regimen also remained improved according to the UPDRS-IV. The beneficial effects of amantadine on motor response complications were maintained for at least 1 year after treatment initiation. Secondary: Dyskinesia ratings from videotapes scored by a second masked rater decreased by 43% with amantadine (3.6 ± 0.6) compared with placebo (6.3 ± 0.8; P<0.05).
Thomas et al.[18] (2004) Amantadine 300 mg per day vs placebo	DB, RCT Patients with severe Parkinson's disease and peak dose or dysphasic dyskinesia with or without pain levodopa-induced dyskinesia. All patients had also been receiving dopamine agonists as part of their treatment	N=40 9 months	Primary: Dyskinesia measured by the Unified Parkinson's Disease Rating Scale (UPDRS), the Dyskinesias Rating Scale (DRS), and an Investigator Global Assessment (IGA) of dyskinesia; change in dyskinesia from study initiation to study end.	Primary: After 15 days of amantadine treatment, there was a reduction by 45% in the DRS total dyskinesia scores (P<0.001). UPDRS scores also decreased significantly with amantadine as compared with placebo (P<0.01). Within the next 8 months, all patients in the amantadine group withdrew from the study as dyskinesia increased according to all scales. By the time of withdrawal there were no significant changes in dyskinesia from study baseline. Three patients in the amantadine group withdrew because of side effects (tachycardia, psychosis, or livedo reticularis. Eighteen patients in the placebo group withdrew from the study within 3 months because dyskinesia had not improved or had gotten worse. The other 2 patients in the placebo group withdrew because of side effects. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Scale score changes and the durations of the "on" and "off" states (periods when levodopa is exerting its effect vs periods when levodopa effect has worn off)	UPDRS scale I-III scores and "off" time were reduced and "on" time was increased in the amantadine group, but this improvement did not persist over the course of the study. Only the initial UPDRS score reductions were statistically significant vs baseline and placebo (P<0.01).
Pappa et al.[5] (2010) Amantadine 100 mg up to 4 times per day for 2 weeks vs placebo for 2 weeks	DB, PC, XO Patients with tardive dyskinesia (TD) and stable psychiatric condition	N=22 4 weeks	Primary: Changes in Abnormal Involuntary Movements Scale (AIMS)	Primary: After amantadine treatment, patients exhibited a reduced average score of total AIMS (from 13.5 to 10.5, P=0.000), of facial and oral AIMS (from 5.5 to 4.2, P=0.002), of extremity AIMS (from 4.18 to 2.8, P=0.000), and of severity AIMS (from 2.04 to 1.54, P=0.002). With amantadine, the average total AIMS reduction was 21.81%. With placebo treatment, no reduction was noted. Amantadine did not alter any of the cognitive measures used in this study, such as MMSE, distress, and BPRS. There were no serious adverse events during amantadine treatment. In the amantadine group, the following adverse events have occurred: insomnia in 3 patients, constipation in 2 patients, and dizziness in 2 patients.
Crosby et al.[15] (2003) Amantadine as treatment for dyskinesia of idiopathic Parkinson's disease vs	MA Patients of all ages with a diagnosis of idiopathic Parkinson's disease who had developed dyskinesia, patients were allowed to be on levodopa	N=53 (3 trials) >4 weeks	Primary: Changes in dyskinesia rating scales, number of withdrawals due to lack of efficacy and/or side effects	Primary: Two of the three studies could not be analyzed for efficacy because of a lack of a washout period prior to the crossover. In regards to the first study, 2 (8%) of the patients withdrew prior to the crossover. In regards to the second study, 4 (22%) of the patients withdrew prior to the crossover. Two of the patients complained of confusion or hallucinations, one complained of nausea, and one complained of a recurrence of pre-existing palpitations. The third study included a one week crossover period so it was eligible to be analyzed for efficacy. No difference was found between amantadine in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				the first or second treatment period. Amantadine was associated with a decrease in dyskinesia severity score by 6.4 points (41%) following the levodopa challenge compared to the placebo arm. One patient experienced reversible edema of both feet during active amantadine treatment.
Paci et al.[20] (2001) Amantadine as adjunctive therapy to current levodopa, carbidopa and dopamine agonist therapy for severe Parkinson's disease	OL Patients with advanced Parkinson's disease complicated by motor fluctuations and levodopa-induced dyskinesia	N=20 8 months	Primary: Unified Parkinson's disease rating scale (UPDRS), Dyskinesias Rating Scale (DRS), and investigator global assessment scale	Primary: Amantadine treatment was associated with a 38% reduction in motor fluctuations (P<0.001) and in the total dyskinesia score compared to baseline. UPDRS subscale IV mean scores decreased from 10 to 6 (P<0.001), and DRS mean scores decreased from 18.5 to 7.5 (P<0.001). The investigator global assessment scale for dyskinesia in patients using amantadine was rated 2.1. After 2-8 months of treatment, dyskinesia scores increased to – 2.2 leading to drug discontinuation in all patients.

Drug regimen abbreviations: BID=twice daily, IV=intravenously, PO=by mouth, QD=once daily
Study abbreviations: DB=double blind, CI=confidence interval, HR=hazard ration, ILI=influenza-like illness, MA=meta-analysis, PC=placebo-controlled, PG=parallel-group, OL=open label, OR=odds ratio, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SC=single-center, 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 9. Relative Cost of the Adamantanes

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amantadine	capsule, syrup, tablet	N/A	N/A	$-$$
Rimantadine	tablet	N/A	N/A	$

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

X. Conclusions

The adamantanes are approved for the treatment and prophylaxis of influenza A virus infections. Amantadine and rimantadine are available in a generic formulation. Guidelines recommend the use of oseltamivir or zanamivir for the treatment and chemoprophylaxis of all influenza subtypes.[11-13] Due to the emergence of resistance, the adamantanes are not effective. Both amantadine and rimantadine have been shown to be effective for the treatment and chemoprophylaxis of influenza A in older clinical trials.[19,23-25,28-31,33] However, there are limited clinical trials that directly compare the efficacy and safety of these agents.[22] Due to the emergence of resistance since these studies were published, providers should refer to current treatment guidelines when making therapeutic decisions about the adamantanes.

Amantadine is also approved for the treatment of parkinsonism and drug-induced extrapyramidal reactions. Guidelines state that amantadine may be used; however, it is not considered a first-line treatment option.[16-17] According to the prescribing information, amantadine is less effective than levodopa for the treatment of

Parkinson's disease.[1-3] For the treatment of drug-induced extrapyramidal reactions, there is a lower incidence of anticholinergic adverse events with amantadine than anticholinergic antiparkinson drugs.[1-3]

Therefore, all brand adamantanes 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 adamantane 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Interferons
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I. Overview

Interferons are naturally occurring proteins with antiviral, antiproliferative and immunoregulatory properties.[1-7] They are produced and secreted in response to viral infections, as well as to a variety of other synthetic and biological inducers. They do not act directly on the virus, but bind to specific receptors on the cell surface, which activates multiple intracellular signaling pathways.

There are 5 interferon products included in this review. Interferon alfa-2b and interferon alfacon-1 are recombinant products, whereas interferon alpha-n3 is a purified, natural, human product. Peginterferon alfa-2a and peginterferon alfa-2b are covalently linked to interferon alfa-2a and interferon alfa-2b molecules with polyethylene glycol. The attachment of polyethylene glycol (pegylation) reduces the rate of absorption and clearance, which extends the half-life of these products.[9] This allows for once weekly dosing as compared to three times per week dosing with the standard interferon alfa products. Pegylation also decreases the immunogenicity of the interferons.[9]

The interferons are primarily used for the treatment of chronic hepatitis B and hepatitis C. The hepatitis B virus (HBV) is a DNA virus that is transmitted through exposure with infected blood and body fluids, and is a leading cause of death from liver disease.[10-11] Acute infection occurs following HBV exposure and the infection generally clears after 1-3 months in immunocompetent individuals. However, chronic infections (≥6 months) are increased in immunocompromised patients and patients who are exposed early in life.[11] Treatment of acute infections is generally supportive and antiviral treatment is not indicated.[10] Treatment of chronic hepatitis B is determined by evidence of viral replication and liver injury.[10]

The hepatitis C virus (HCV) is a RNA virus that is also transmitted through exposure with infected blood.[12-13] Once infected, HCV causes hepatic inflammation and steatosis.[12] With persistent infections, patients may develop hepatic fibrosis, which can lead to cirrhosis and an increased risk for hepatocellular carcinoma. There are six genotypes of HCV; genotype 1 is the most prevalent in the U.S.[12] There are differences in response to interferon-based therapy among the genotypes.[13] Genotype 1 is associated with a lower response to therapy and a longer duration of therapy is required.

The interferons that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. None of the interferons are available in a generic formulation. This class was last reviewed in November 2009.

Table 1. Interferons Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Interferon alfa-2b	injection	Intron® A	none
Interferon alfacon-1	injection	Infergen®	Infergen®
Interferon alfa-n3	injection	Alferon N®	none
Peginterferon alfa-2a	injection	Pegasys®	none
Peginterferon alfa-2b	injection	PegIntron®	PegIntron®

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the interferons are summarized in Table 2.

Table 2. Treatment Guidelines Using the Interferons

Clinical Guideline	Recommendation(s)

American Association for the Study of Liver Diseases (AASLD): **Chronic Hepatitis B Update**[18] **(2009)**	General Information
	• The aims of treatment of chronic hepatitis B are to achieve sustained suppression of HBV replication and remission of liver disease. The ultimate goal is to prevent cirrhosis, hepatic failure and hepatocellular carcinoma.
	• Parameters used to assess treatment response include normalization of serum ALT, decrease in serum HBV DNA level, loss of hepatitis B e antigen (HBeAg) with or without detection of anti-HBe, and improvement in liver histology.
	• Responses to antiviral therapy of chronic hepatitis B are categorized as biochemical (BR), virologic (VR), or histologic (HR), and as on-therapy or sustained off therapy.
	• Seven therapeutic agents have been approved for the treatment of adults with chronic hepatitis B in the United States. While interferons are administered for predefined durations, the nucleoside/nucleotide analogues (NAs) are usually administered until specific endpoints are achieved. The difference in approach is related to the additional immune modulatory effects of the interferons.
	General Treatment Recommendations
	• Patients with HBeAg-positive chronic hepatitis B with ALT >2 times normal or moderate/severe hepatitis on biopsy and HBV DNA >20,000 IU/mL should be considered for treatment.
	  o Treatment should be delayed for 3 to 6 months in persons with compensated liver disease to determine if spontaneous HBeAg seroconversion occurs.
	  o Patients with icteric ALT flares should be promptly treated.
	  o Treatment may be initiated with any of the 7 approved antiviral medications, but peginterferon alfa, tenofovir or entecavir are preferred.
	  o Clinical trials suggest that the efficacy of peginterferon alfa is similar to or slightly better than standard interferon alfa.
	• Patients with HBeAg-positive chronic hepatitis B and ALT persistently normal or minimally elevated (<2 times normal) generally should not be initiated on treatment.
	• Children with elevated ALT >2 times normal should be considered for treatment if ALT levels remain elevated at this level for longer than 6 months.
	  o Treatment may be initiated with interferon alfa or lamivudine.
	• Patients with HBeAg-negative chronic hepatitis B (serum HBV DNA >20,000 IU/mL and elevated ALT>2 times normal) should be considered for treatment.
	  o Liver biopsy may be considered for HBeAg-negative patients with lower HBV DNA levels (2,000-20,000 IU/mL) and borderline normal or minimally elevated ALT levels.
	  o Treatment may be initiated if there is moderate/severe inflammation or significant fibrosis on biopsy.
	  o Treatment may be initiated with any of the 7 approved antiviral medications, but peginterferon alfa, tenofovir or entecavir are preferred in view of the need for long-term

Clinical Guideline	Recommendation(s)
	treatment. • Patients who failed to respond to prior interferon alfa (standard or pegylated) therapy may be retreated with nucleoside/nucleotide analogues (NA). • Patients who failed to achieve primary response as evidenced by <2 log decrease in serum HBV DNA level after at least 6 months of NA therapy should be switched to an alternative treatment or receive additional treatment. • In patients with inactive HBsAg carrier state, antiviral treatment is not indicated, but these patients should be monitored. <u>Patients Who Develop Breakthrough Infection While Receiving NA Therapy</u> • All patients with virologic breakthrough should be considered for rescue therapy. • For patients in whom there was no clear indication for hepatitis B treatment and who continue to have compensated liver disease, withdrawal of therapy may be considered but these patients need to be closely monitored and treatment reinitiated if they experience severe hepatitis flares. <u>Treatment of Patients with Lamivudine (or telbivudine)-resistant HBV</u> • If adefovir is used, lamivudine (or telbivudine) should be continued indefinitely to decrease the risk of hepatitis flares during the transition period and to reduce the risk of subsequent adefovir resistance. • If tenofovir is used, continuation of lamivudine (or telbivudine) is recommended to decrease the risk of subsequent antiviral resistance. • If entecavir is used, lamivudine or telbivudine should be stopped as continued presence of lamivudine- (or telbivudine-) resistant mutations will increase the risk of entecavir resistance. Entecavir is not an optimal therapy because of increasing risk of resistance to entecavir over time. <u>Treatment of Patients with Adefovir-resistant HBV</u> • In patients with no prior exposure to other NA, lamivudine, telbivudine or entecavir may be added. Alternatively, adefovir may be stopped and tenofovir plus lamivudine or emtricitabine may be used. • In patients with prior lamivudine resistance in whom lamivudine had been stopped when treatment was switched to adefovir, adefovir may be stopped and tenofovir plus lamivudine, emtricitabine or entecavir may be used but the durability of response to this combination is unknown. <u>Treatment of Patients with Entecavir-resistant HBV</u> • Adefovir or tenofovir can be used as it has been shown to have activity against entecavir-resistant HBV in *in vitro* studies, but clinical data are lacking. <u>Treatment of Patients with Compensated Cirrhosis</u> • Treatment should be considered for patients with ALT >2 times normal, and for patients with normal or minimally elevated ALT if serum HBV DNA levels are high (>2,000 IU/mL). • Patients with compensated cirrhosis are best treated with NAs because of the risk of hepatic decompensation associated with interferon alfa–related flares of hepatitis. In view of the need for long-term therapy, tenofovir or entecavir is preferred. <u>Treatment of Patients with Decompensated Cirrhosis</u> • Treatment should be promptly initiated with a NA that can produce rapid viral suppression with low risk of drug resistance.

Clinical Guideline	Recommendation(s)
	• Lamivudine or telbivudine may be used as initial treatment in combination with adefovir or tenofovir to reduce the risk of drug resistance. • Entecavir or tenofovir alone would be an appropriate treatment in this setting but clinical data documenting their safety and efficacy in patients with decompensated cirrhosis are lacking. • Treatment should be coordinated with a transplant center. • Interferon alfa or peginterferon alfa should not be used in patients with decompensated cirrhosis. <u>Treatment Duration</u> • The recommended treatment duration for HBeAg-positive chronic hepatitis B is 16 weeks for standard interferon alfa and 48 weeks for peginterferon alfa. • The recommended treatment duration for HBeAg-negative chronic hepatitis B is 48 weeks for both standard and peginterferon alfa. • Treatment with NAs should be continued until the patient has achieved HBeAg seroconversion and undetectable serum HBV (for patients with HBeAg-positive chronic hepatitis B). For patients with HBeAg-negative chronic hepatitis B, treatment should be continued until the patient has achieved HBsAg clearance. For patients with compensated cirrhosis, treatment should be received long-term. However, treatment may be stopped in HBeAg-positive patients if they have confirmed HBeAg seroconversion and have completed at least 6 months of consolidation therapy and in HBeAg-negative patients if they have confirmed HBsAg clearance. For patients with decompensated cirrhosis and recurrent hepatitis B post–liver transplantation, life-long treatment is recommended. <u>Recommendations for Treatment of Patients with HBV/HIV Coinfection</u> • Patients who meet criteria for chronic hepatitis B should be treated. • Patients who are not on HAART and are not anticipated to require HAART in the near future should be treated with an antiviral therapy that does not target HIV, such as peginterferon alfa or adefovir. Although telbivudine does not target HIV, it should not be used in this circumstance. • Patients in whom treatment for both HBV and HIV is planned should receive therapies that are effective against both viruses: lamivudine plus tenofovir or emtricitabine plus tenofovir are preferred. • Patients who are already on effective HAART that does not include a drug active against HBV may be treated with peginterferon alfa or adefovir. • In patients with lamivudine resistance, tenofovir should be added. <u>Recommendations for Treatment of Hepatitis B Carriers Who Require Immunosuppressive or Cytotoxic Therapy</u> • Prophylactic antiviral therapy is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy. • Patients with baseline HBV DNA<2,000 IU/mL level should continue treatment for 6 months after completion of chemotherapy or immunosuppressive therapy. • Patients with high baseline HBV DNA (>2,000 IU/mL) level should continue treatment until they reach treatment endpoints as in immunocompetent patients. • Lamivudine or telbivudine can be used if the anticipated duration of treatment is short (<12 months) and baseline serum HBV DNA is not

Clinical Guideline	Recommendation(s)
	detectable. • Tenofovir or entecavir is preferred if longer duration of treatment is anticipated. • Interferon alfa should be avoided in view of the bone marrow suppressive effect. <u>Recommendations for Treatment of Patients with Acute Symptomatic Hepatitis B</u> • Treatment is only indicated for patients with fulminant hepatitis B and those with protracted, severe acute hepatitis B. • Lamivudine or telbivudine may be used when the anticipated duration of treatment is short; otherwise, entecavir is preferred. • Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation. • Interferon alfa therapy is contraindicated.
American Association for the Study of Liver Diseases (AASLD): **Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection**[8] **(2011)**	<u>General Considerations</u> • The optimal therapy for genotype 1, chronic HCV infection is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin. • Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin. <u>Treatment-Naive Patients:</u> • The recommended dose of boceprevir is 800 mg administered with food three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 24-44 weeks preceded by 4 weeks of lead-in treatment with peginterferon alfa and ribavirin alone. • Patients without cirrhosis treated with boceprevir, peginterferon, and ribavirin, preceded by 4 weeks of lead-in peginterferon and ribavirin, whose HCV RNA level at weeks 8 and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (4 weeks lead-in with peginterferon and ribavirin followed by 24 weeks of triple therapy). • Treatment with all three drugs (boceprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24. • The recommended dose of telaprevir is 750 mg administered with food (not low-fat) three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12-36 weeks of peginterferon alfa and ribavirin. • Patients without cirrhosis treated with telaprevir, peginterferon, and ribavirin, whose HCV RNA level at weeks 4 and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks. • Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peginterferon and ribavirin should receive therapy for a duration of 48 weeks. • Treatment with all three drugs (telaprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >1,000 IU/mL at treatment weeks 4 or 12 and/or detectable at treatment week 24. <u>Treatment-Experienced Patients</u> • Re-treatment with boceprevir or telaprevir, together with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin. • Re-treatment with telaprevir, together with peginterferon alfa and

Clinical Guideline	Recommendation(s)
	weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peginterferon alfa and/or weight-based ribavirin. • Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers, may be considered for partial responders, but cannot be recommended for null responders. • Patients re-treated with boceprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. • Patients re-treated with telaprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 1,000 IU at weeks 4 or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. • Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose. • Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (>1 log increase in serum HCV RNA above nadir) is observed. • Patients who fail to have a virological response, who experience virological breakthrough, or who relapse on one protease inhibitor should not be re-treated with the other protease inhibitor.
American Association for the Study of Liver Diseases (AASLD): **Diagnosis, Management, and Treatment of Hepatitis C: Update[17] (2009)**	General Information • The goal of therapy is to prevent complications and death from HCV infection. Treatment responses are defined by a surrogate virological parameter rather than a clinical endpoint. Short-term outcomes can be measured biochemically (normalization of serum ALT levels), virologically (absence of HCV RNA from serum by a sensitive PCR-based assay), and histologically (point improvement in necroinflammatory score with no worsening in fibrosis score). • Several types of virological responses may occur, labeled according to their timing relative to treatment. The most important is the sustained virological response (SVR), defined as the absence of HCV RNA from serum by a sensitive PCR assay 24 weeks following discontinuation of therapy (virological cure). Undetectable virus at the end of either a 24-week or 48-week course of therapy is referred to as an end-of-treatment response (ETR). An ETR does not accurately predict that an SVR will be achieved, but is necessary for it to occur. • The currently recommended therapy of chronic HCV infection is the combination of a pegylated interferon alfa and ribavirin. • Treatment decisions should be individualized based on the severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions, and the patient's readiness for treatment. Genotype1 and Genotype 4 HCV Infection • Treatment with peginterferon plus ribavirin should be planned for 48 weeks. • Treatment may be discontinued in patients who do not achieve an early virological response (EVR; >2 log reduction in HCV RNA at week 12 of treatment). • Patients who do not achieve a complete EVR (undetectable HCV RNA at week 12 of treatment) should be re-tested at week 24, and if HCV

Clinical Guideline	Recommendation(s)
	RNA remains positive, treatment should be discontinued. • For patients with genotype 1 infection who have delayed virus clearance (HCV RNA test becomes negative between weeks 12 and 24), consideration should be given to extending therapy to 72 weeks. Genotype 2 or Genotype 3 HCV Infection • Treatment with peginterferon plus ribavirin should be administered for 24 weeks. Retreatment • Retreatment with peginterferon plus ribavirin in patients who did not achieve an SVR after a prior full course of peginterferon plus ribavirin is not recommended, even if a different type of peginterferon is administered. • Retreatment with peginterferon plus ribavirin can be considered for non-responders or relapsers who have previously been treated with non-pegylated interferon with or without ribavirin, or with peginterferon monotherapy, particularly if they have bridging fibrosis or cirrhosis. • Maintenance therapy is not recommended for patients with bridging fibrosis or cirrhosis who have failed a prior course of peginterferon and ribavirin. Treatment of Persons with Normal Serum Aminotransferase Values • Regardless of the serum alanine aminotransferase level, the decision to initiate therapy with pegylated interferon and ribavirin should be individualized based on the severity of liver disease by liver biopsy, the potential for serious side effects, the likelihood of response, and the presence of comorbid conditions. • The treatment regimen for HCV-infected persons with normal aminotransferase levels should be the same as that used for persons with elevated serum aminotransferase levels. Treatment of Children • Children aged 2-17 years who are infected with HCV should be considered appropriate candidates for treatment using the same criteria as that used for adults. • Children should be treated with pegylated interferon alfa-2b, 60 mcg/m^2 weekly in combination with ribavirin, 15 mg/kg daily for a duration of 48 weeks. Treatment of HIV-infected Persons • Hepatitis C should be treated in the HIV/HCV co-infected patient in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of morbidity from the adverse effects of therapy. • Initial treatment of hepatitis C in most HIV-infected patients should be peginterferon alfa plus ribavirin for 48 weeks at doses recommended for HCV mono-infected patients. • When possible, patients receiving zidovudine (AZT) and especially didanosine (ddI) should be switched to an equivalent antiretroviral agent before beginning therapy with ribavirin. • HIV-infected patients with decompensated liver disease (CTP Class B or C) should not be treated with peginterferon alfa and ribavirin and may be candidates for liver transplantation.
American Gastroenterological Association (AGA): **Medical Position Statement on the Management of Hepatitis C**[16]	• Therapy is indicated for previously untreated patients with chronic hepatitis C, circulating HCV RNA, elevated aminotransferase levels, evidence on liver biopsy of moderate to severe hepatitis grade and stage, and compensated liver disease.

Clinical Guideline	Recommendation(s)

(2006)	• Patients with normal ALT activity are candidates for antiviral therapy or for monitoring without intervention, as determined on an individual basis and as influenced by patient factors such as motivation, genotype, histologic activity, and fibrosis.
	• Patients with compensated cirrhosis who can tolerate therapy are candidates for treatment.
	• The treatment of choice is pegylated interferon alfa plus ribavirin.
	• Patients with genotypes 1 and 4 require 48 weeks of therapy with pegylated interferon and high daily doses of ribavirin (1,000–1,200 mg, depending on weight).
	• Patients with genotypes 2 and 3 can be treated for only 24 weeks with pegylated interferon and with 800 mg of ribavirin daily, with the following exceptions:
	  o A longer duration of therapy may be considered on an individual patient basis taking into account factors such as elevated viral level, cirrhosis, or delayed response to therapy.
	  o 12 weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week 4.
	  o Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks.
	• Therapy with peginterferon alfa and ribavirin should be strongly considered for patients who experienced a relapse after a course of standard interferon alfa/ribavirin combination therapy, while a longer duration of therapy in patients who experienced a relapse after 12 months of treatment with peginterferon alfa plus ribavirin is of unproven efficacy.
	• For children, the general principles of management are the same as those for adults, except that treatment is not recommended for children younger than 3 years.
	• For HIV-infected individuals, the optimal therapy consists of peginterferon alfa plus ribavirin for 48 weeks, regardless of genotype. Because of potential drug-drug interactions in patients on HIV treatment regimens that include didanosine, HIV regimens should be altered in those starting combination therapy for HCV infection. If didanosine is critical to the HIV regimen, ribavirin should be avoided.

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[14] (2008)**	<u>Treatment of Genital Warts</u> • Intralesional interferon has been used for the treatment of genital warts but due to difficult administration and potential for systemic side effects, it is not recommended for first-line treatment. The overall efficacy of interferon is no better than other therapies and it has not been specifically studied for genital warts among HIV-infected persons. <u>Treatment of Hepatitis B Virus Coinfection in Patients Not Receiving Antiretroviral Therapy</u> • For patients with CD4+ counts >350 cells/µL who are not receiving ART but meet criteria for HBV treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of HBV DNA levels and follow-up to evaluate for HBeAg seroconversion. However, early initiation of ART should also be considered for HIV/HBV-coinfected persons with CD4+ counts >350 cells/µL. <u>Treatment of Hepatitis B Virus Coinfection in Patients Who Require Antiretroviral Therapy</u>

Clinical Guideline	Recommendation(s)

	• For HIV-infected persons, some experts recommend combination therapy with two agents active against HBV to reduce the risk of HBV drug resistance, although there are no results from controlled trials as yet to support this strategy.
	• Among patients infected with HBV, HCV, and HIV, consideration of the need for ART should be the first priority. If ART is not required, interferon-based therapy, which suppresses both HCV and HBV, should be considered. If interferon-based therapy for HCV has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended.
	<u>Treatment of Hepatitis C Coinfection</u>
	• Antiviral treatment for HCV infection should be considered for all HIV-infected persons with acute or chronic HCV infection. In the absence of contraindications to peginterferon and/or ribavirin, treatment for HCV infection should be routinely offered to persons in whom the potential benefits of therapy are judged to outweigh the potential risks, including (but not limited to) persons with:
	  o HCV genotype 2 or 3 infection
	  o HCV genotype 1 infection with a low HCV RNA level (<800,000 IU/mL)
	  o Significant hepatic fibrosis (bridging fibrosis or cirrhosis)
	  o Stable HIV infection not requiring ART
	  o Acute HCV infection (<6 months duration)
	  o Cryoglobulinemic vasculitis
	  o Cryoglobulinemic membranoproliferative glomerulonephritis
	  o Strong motivation to treat their HCV infection
	• On the basis of well-designed, randomized, controlled trials, peginterferon plus ribavirin is the recommended treatment for hepatitis C in HIV-infected persons.
	• For all HCV genotypes, the recommended treatment regimen includes either peginterferon alfa-2a or peginterferon alfa-2b plus oral ribavirin for a total duration of 48 weeks.
	• Patients with contraindications to the use of ribavirin can be treated with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower SVR rates are expected in persons not receiving ribavirin.

Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines[15] (2010)**	<u>Genital warts</u> • No evidence exists to identify one treatment as more efficacious than another and no treatment is ideal for all patients with genital warts. • Treatment selection may be based on wart size and number, anatomic site of wart, wart morphology, and adverse effects of treatment. • Interferon therapy is not recommended as a primary modality because of inconvenient routes of administration, frequent office visits, and the association between its use and a high frequency of adverse effects. <u>Hepatitis B</u> • No specific therapy is available for persons with acute hepatitis B; treatment is supportive. • Therapeutic agents approved by FDA for treatment of chronic hepatitis B can achieve sustained suppression of HBV replication and remission of liver disease in some persons. <u>Hepatitis C</u> • Combination therapy with pegylated interferon and ribavirin is the treatment of choice for patients with chronic hepatitis C.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the interferons are noted in Table 3. 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 3. FDA-Approved Indications for the Interferons[1-7]

Indication	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Cancer					
Adjuvant to surgical treatment in patients with malignant melanoma who are free of disease but at high risk for systemic recurrence, within 56 days of surgery	✔				
Initial treatment of clinically aggressive follicular Non-Hodgkin's Lymphoma in conjunction with anthracycline-containing combination chemotherapy	✔				
Treatment of hairy cell leukemia	✔				
Treatment of selected patients with AIDS-related Kaposi's sarcoma	✔				
Condylomata Acuminata					
Intralesional treatment of selected patients with condylomata acuminata involving external surfaces of the genital and perianal areas	✔				
Intralesional treatment of refractory or recurring external condylomata acuminata			✔		
Hepatitis B					
Treatment of chronic hepatitis B in patients with compensated liver disease who have been serum HBsAg positive for at least 6 months and have evidence of HBV replication with elevated serum ALT	✔				
Treatment of patients with HBeAg positive and HBeAg negative chronic hepatitis B infection who have compensated liver disease and evidence of viral replication and liver inflammation				✔	
Hepatitis C					
Treatment of chronic hepatitis C in patients with compensated liver disease who have a history of blood or blood-product exposure and/or are HCV antibody positive	✔				
Treatment of chronic hepatitis C in patients with compensated liver disease		✔			
Treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha				✔	
Treatment of chronic hepatitis C in patients with compensated liver disease					✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the interferons are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Interferons[1-7]

Generic Name(s)	Bioavailability (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Interferon alfa-2b	>90	Kidney, extensive Liver, minor	Not reported	2-3
Interferon alfacon-1	83-100	Not reported	Renal	1.3-3.4
Interferon alfa-n3	Not reported	Kidney, extensive Liver, minor	Not reported	4.43-6.76
Peginterferon alfa-2a	>60	Liver	Renal	84-353
Peginterferon alfa-2b	Not reported	Liver	Renal	22-60

V. Drug Interactions

Significant drug interactions with the interferons are listed in Table 5.

Table 5. Significant Drug Interactions with the Interferons[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Interferon alfa-2b	2	Fluorouracil	Interferon alfa-2b may enhance the pharmacologic and toxic effects of fluorouracil.
Interferons	2	Telbivudine	Coadministration may increase the risk and severity of telbivudine-related peripheral neuropathy.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the interferons are listed in Table 6. The boxed warning for the interferons is listed in Table 7.

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

Adverse Events	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Cardiovascular					
Arrhythmia	<5	✔	-	✔	✔
Cardiomyopathy	2	✔	-	✔	✔
Chest pain	-	5-13	10	<1	6-8
Flushing	-	4-13	1	-	4-6
Hypertension	-	-	-	✔	✔
Hypotension	<5	✔	6	-	✔
Myocardial infarction	✔	✔	-	✔	✔
Tachycardia	<5	✔	-	-	✔
Central Nervous System					
Abnormal thinking	-	8-20	-	-	-
Aggressive behavior	<5	✔	-	<1	✔
Agitation/irritability	1-22	17-21	-	19-33	14-47
Amnesia	1-14	2-10	-	-	-
Anxiety	1-9	9-19	-	✔	28-47
Apathy	-	✔	-	-	-
Ataxia	-	✔	-	-	-
Bipolar disorder	-	-	-	✔	✔
Concentration impaired	<1-14	-	1	8-10	10-17
Confusion	<1-12	4-5	-	-	-
Convulsions	-	✔	-	-	✔
Delusions	-	✔	-	-	-
Depression	3-40	18-26	2	18-20	29-59
Drowsiness	1-33	4-7	-	3-5	-
Dizziness	7-23	18-25	9	13-23	12-35
Fatigue	8-96	65-71	6-14	24-67	52-94
Gait abnormal	-	✔	-	-	-
Hallucinations	-	✔	-	✔	✔
Headache	21-62	78-82	10-31	27-60	56-70
Hemorrhagic cerebrovascular events	✔	✔	-	<1	✔
Homicidal ideation	✔	✔	-	-	✔
Insomnia	<1-12	24-39	2	19-30	23-40

Adverse Events	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Ischemic cerebrovascular events	✔	✔	-	✔	✔
Lethargy	8-96	2-71	65	56-65	52-66
Loss of consciousness	-	✔	-	-	-
Malaise	8-96	2-11	65	56-65	4-7
Mania	-	-	-	✔	✔
Memory impairment	-	✔	-	-	✔
Migraine	-	-	-	-	✔
Nervousness	-	16-31	-	19-33	4-6
Paresthesia	1-21	9-13	1	-	21
Psychosis	-	-	-	<1	✔
Seizure	-	-	-	✔	-
Shivering	-	-	14-87	-	-
Somnolence	1-33	4-7	10	3-5	-
Speech disorder	-	✔	-	-	-
Suicidal behavior	<5	✔	-	<1	✔
Tremors	-	✔	-	-	-
Vertigo	-	-	-	-	✔
Dermatological					
Alopecia	8-38	10-14	-	18-28	22-36
Diaphoresis	-	11-13	2	6	6-11
Dry skin	-	2-6	-	4-10	11-24
Eczema	-	-	-	1-5	-
Erythema multiforme	✔	-	-	-	29
Exfoliative dermatitis	-	-	-	8-16	-
Herpes labialis	-	-	1	-	-
Phototoxicity	-	-	-	-	<1
Pruritus	-	10-14	2	12-19	12-29
Psoriasis	<5	-	✔	-	✔
Pyoderma gangrenosum	-	✔	-	-	-
Rash	-	10-13	1	5-8	6-24
Stevens-Johnson syndrome	✔	-	-	✔	✔
Toxic epidermal necrolysis	✔	✔	-	-	✔
Urticaria	-	-	-	-	<1
Vasculitis	-	-	-	-	<1
Endocrine and Metabolic					
Diabetes	<5	✔	-	<1	✔
Gynecomastia	<5	-	-	-	-

Adverse Events	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Thyroid dysfunction	-	-	✔	-	-
Thyroiditis	-	-	-	✔	✔
Gastrointestinal					
Abdominal cramping	1-23	24-41	-	-	-
Abdominal discomfort	1-23	24-41	-	-	-
Abdominal pain	1-23	24-41	-	8-26	13-21
Anorexia	1-69	14-24	68	16-24	20-69
Constipation	<1-14	9-10	-	-	1-5
Diarrhea	2-45	22-29	6	11-31	18-37
Dry/painful mouth	-	-	6	4-6	6-12
Dyspepsia	-	10-21	3	49	6-9
Flatulence	-	5-8	3	-	-
Gastrointestinal bleeding	-	✔	-	<1	-
Hemorrhagic colitis	-	✔	-	<1	✔
Ischemic colitis	-	✔	-	<1	✔
Nausea	17-66	30-40	48	5-25	26-64
Pancreatitis	✔	✔	-	<1	<1
Taste alterations	<1-24	-	1	-	<1-38
Vomiting	66	11-13	3-29	5-25	7-26
Weight decrease	<1-10	16-22	-	4-16	11-29
Genitourinary					
Impaired spermatogenesis	✔	-	-	-	-
Interstitial nephritis	-	-	-	✔	✔
Menstrual cycle abnormalities	-	-	-	-	4-7
Nephrotic syndrome	✔	-	-	-	-
Polyuria	<5-10	-	-	-	-
Proteinuria	<5	-	-	-	7
Renal failure	✔	✔	-	-	✔
Renal insufficiency	✔	-	✔	-	✔
Hematological					
Anemia	<5	✔	7	2-14	11-12
Aplastic anemia	✔	✔	-	<1	-
Hematocrit decreased	-	✔	7	17-52	✔
Hemoglobin decreased	-	✔	7	17-52	✔
Hemolytic anemia	<5	30	-	-	-
Leukopenia	-	24-34	3	-	<1-10
Lymphopenia	-	✔	-	3-14	-

Adverse Events	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Neutropenia	9-92	21-27	-	21-40	6-33
Platelets increased or decreased	-	✔	3	33-52	-
Pure red cell aplasia	-	-	-	✔	-
Thrombocytopenia	✔	18-19	-	5-8	5-7
Thrombocytopenic purpura	✔	✔	-	✔	✔
Hepatic					
Ascites	-	✔	-	-	-
Fatty liver	-	-	-	✔	-
Hepatic encephalopathy	✔	✔	-	-	-
Hepatomegaly	-	-	-	-	4-6
Hepatotoxicity	✔	✔	-	✔	-
Jaundice	<5	✔	-	-	-
Laboratory Test Abnormalities					
Albuminuria	<5	-	-	-	-
Alkaline phosphatase increased	-	-	8	-	23
ALT increased	<5-63	✔	3	✔	10-77
AST increased	<5-63	✔	3	✔	10-77
Bilirubin increased or decreased	<5	✔	4	-	-
BUN increased	<5	-	-	-	-
Cholesterol increased	✔	✔	✔	20-36	✔
Hyperglycemia	<5	✔	✔	-	<1
Hyperkalemia	<5	-	✔	-	-
Hyperthyroidism	<5	✔	-	1-2	3
Hypocalcemia	<5	-	✔	-	-
Hypothyroidism	<5	✔	-	3-4	5
LDH increased	<5	-	-	-	-
Triglycerides increased	✔	✔	✔	20-36	✔
Uric acid increased	-	✔	-	-	33-38
Musculoskeletal					
Arthralgia	3-19	43-51	5-10	22-28	17-51
Arthritis	-	✔	-	-	-
Asthenia	5-63	7-10	-	-	-
Back pain	1-15	23-42	4	5-9	-
Bone pain	-	10-14	-	-	-
Limb pain	-	13-26	-	-	-
Myalgia	16-75	51-58	16-45	26-51	17-68
Myesthenia gravis	1-21	-	-	-	-

Adverse Events	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Myositis	✔	✔	-	<1	✔
Neck pain	-	5-14	-	-	-
Pain	3-18	39-54	-	10-11	21-28
Rhabdomyolysis	✔	✔	-	✔	✔
Rigor	-	-	-	25-47	21-63
Respiratory					
Asthma	≤5	-	-	-	-
Bronchiolitis obliterans	✔	✔	-	-	-
Bronchitis	≤5-10	✔	-	-	-
Bronchoconstriction	✔	✔	-	-	-
Cough	<1-34	11-22	-	4-10	5-23
Dyspnea	<1-34	7-8	-	4-13	4-26
Epistaxis	<5-7	-	✔	-	-
Interstitial pneumonitis	✔	✔	-	✔	✔
Pharyngitis	<1-34	17-34	✔	-	10-12
Pneumonia	✔	✔	-	<5	✔
Pulmonary embolism	-	-	-	<1	-
Pulmonary hypertension	✔	✔	-	-	-
Pulmonary infiltrates	✔	✔	-	✔	-
Rhinitis	-	7-13	-	-	2-8
Sarcoidosis	✔	✔	-	-	-
Sinusitis	<1-34	12-17	-	-	6-7
Respiratory failure	✔	-	-	-	-
Respiratory tract infections	-	16-31	-	-	-
Special Senses					
Conjunctivitis	-	-	-	-	4
Decrease or loss of vision	✔	✔	6	✔	✔
Hearing impairment	-	-	-	✔	✔
Hearing loss	✔	✔	-	✔	✔
Macular edema	✔	✔	-	✔	✔
Optic edema	✔	3-9	-	✔	✔
Optic neuritis	✔	✔	-	✔	✔
Papilledema	✔	✔	-	✔	-
Retinal artery or vein thrombosis	✔	✔	-	✔	✔
Retinal detachment	✔	✔	-	✔	-
Retinal hemorrhages and cotton wool spots	✔	✔	-	✔	✔
Retinopathy	✔	✔	-	✔	✔

Adverse Events	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Taste/smell disturbances	-	3-5	-	-	23
Visual disturbances	<5	3-5	1	4-5	2-5
Other					
Anaphylaxis	<5	3-7	-	✔	✔
Angioedema	✔	✔	-	-	✔
Bacterial, fungal and viral infections	✔	✔	✔	<5	✔
Chills	45-54	-	14-87	-	-
Drug addiction/overdose	✔	✔	-	-	✔
Fever	34-94	55-61	40-81	24-54	22-75
Flu-like syndrome	20-100	8-15	✔	✔	✔
Hypersensitivity reactions	✔	✔	-	✔	✔
Injection site reaction	✔	17-23	10	10-31	47-75
Lupus erythematosus	✔	-	-	-	-
Peripheral neuropathy	-	✔	-	✔	✔
Raynaud's phenomenon	✔	-	-	-	-
Rheumatoid arthritis	✔	-	-	-	✔
Sepsis	-	✔	-	<5	✔
SIADH	<5	-	✔	-	-
Systemic lupus erythematosus	✔	-	-	✔	✔
Vasculitis	✔	-	-	-	-

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for the Interferons[1]

WARNING
Risk of serious disorders: May cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor patients closely with periodic clinical and laboratory evaluations. Withdraw therapy in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping therapy. **Use with ribavirin:** Ribavirin may cause birth defects and/or death of the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen.

VII. Dosing and Administration

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

Table 8. Usual Dosing Regimens for the Interferons[1-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Interferon alfa-2b	AIDS-Related Kaposi's Sarcoma: 30 MIU/m^2 SC or IM TIW until disease progression or maximal response after 16 weeks Condylomata Acuminata: 1.0 MIU/lesion TIW on alternative days for 3 weeks, for a maximum of 5 lesions in a single course. An additional course may be administered at 12 to 16 weeks. Follicular Lymphoma: 5 MIU SC TIW for up to 18 months used in conjunction with anthracycline-containing chemotherapy and following completion of chemotherapy Hairy Cell Leukemia: 2 MIU/m^2 IM or SC TIW for up to 6 months Hepatitis B (Chronic): 5 MIU daily or 10 MIU TIW for 16 weeks Hepatitis C (Chronic): 3 MIU TIW SC or IM up to 18 to 24 months. Patients who do not normalize their ALT after 16 weeks should be considered for treatment discontinuation. Malignant Melanoma:	Hepatitis B (Chronic): ≥1 year of age: 3 MIU/m^2 SC TIW for 1 week, then 6 MIU/m^2 TIW for a total duration of 16 to 24 weeks	Injection: 6 MIU/ml 10 MIU/ml 18 MIU/ml 50 MIU/ml Pen Injection Kit: 3 MIU/0.2 ml 5 MIU/0.2 ml 10 MIU/0.2 ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Induction: 20 MIU/m^2 IV daily for 5 consecutive days per week for 4 weeks; maintenance, 10 MIU/m^2 SC TIW for 48 weeks		
Interferon alfacon-1	Hepatitis C (Chronic): Monotherapy: initial, 9 mcg SC TIW for 24 weeks. If no response or relapse upon discontinuation, 15 mcg SC TIW for up to 48 weeks Combination with ribavirin: 15 mcg SC once daily with ribavirin 500-600 mg BID	Safety and efficacy in children have not been established.	Injection: 9 mcg/0.3 ml 15 mcg/0.5 ml
Interferon alfa-n3	Condylomata Acuminata: 0.05 mL/wart twice weekly for up to 8 weeks	Safety and efficacy in children have not been established.	Injection: 5 MIU/ml
Peginterferon alfa-2a	Hepatitis B (Chronic): 180 mcg SC once weekly for 48 weeks Hepatitis C (Chronic): Monotherapy: 180 mcg SC once weekly for 48 weeks Combination with ribavirin: 180 mcg SC once weekly for 24 weeks (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4)	Hepatitis C (Chronic): ≥5 years of age: 180 mcg/1.73 m^2 x BSA SC once weekly; maximum, 180 mcg	Injection: 180 mcg/ml Kit: 180 mcg/0.5 ml
Peginterferon alfa-2b	Hepatitis C (Chronic): Monotherapy: 1 mcg/kg SC once weekly for 1 year Combination with ribavirin: 1.5 mcg/kg SC once weekly for 24 weeks (genotypes 2/3) or 48 weeks (genotype 1). The treatment duration for patients who previously failed therapy is 48 weeks, regardless of HCV genotype.	Hepatitis C (Chronic): ≥3 years of age: Combination with ribavirin: 60 mcg/m^2 SC once weekly for 24 weeks (genotypes 2 and 3) or 48 weeks (genotype 1)	Kit: 50 mcg/0.5 ml 80 mcg/0.5 ml 120 mcg/0.5 ml 150 mcg/0.5 ml Pen Injection Kit: 50 mcg/0.5 ml 80 mcg/0.5 ml 120 mcg/0.5 ml 150 mcg/0.5 ml

Drug dosing abbreviations: IM= intramuscularly, IV=intravenously, MIU=million international units, SC=subcutaneously, TIW= three times weekly

VIII. Effectiveness

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

Table 9. Comparative Clinical Trials with the Interferons

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hepatitis B				
Sun et al.[46] (2011) Peginterferon alfa-2a 180 mcg/week x 48 weeks vs adefovir 10 mg daily x 72 weeks	OL, RCT Adult patients with chronic hepatitis B with lamivudine resistance	N=235 6 months posttreatment	Primary: Rate of HBeAg seroconversion at week 72	Primary: At 6 months posttreatment, significantly more patients in the peginterferon group achieved HBeAg seroconversion compared to adefovir (14.6% vs 3.8%, P=0.01). Overall, the response rate for all patients with lamivudine-resistant HBV was very low at any time period during the study. Patients taking peginterferon alfa-2a experienced a serious adverse event rate of 7.8% compared to 2.4% in the adefovir-treated group.
Wong et al.[39] (2010) Peginterferon alfa-2b 1.5 mcg/kg/week for 32 weeks plus lamivudine 100 mg daily for 52 to 104 weeks	2 RCTs (Pooled analysis) Adult Chinese patients with positive HBsAg for >6 months	N=85 5 years	Primary: Virological response at 5 years (defined as HBeAg seroconversion and HBV DNA reduction to <10,000 copies/ml) Secondary: Serum HBV DNA reduction to <10,000 copies/ml and undetectable level (<100 copies/ml), HBsAg seroclearance, normalization of ALT	Primary: Overall, 28 patients (33%) had a sustained virologic response at the end of the treatment period, and 25 (29%) has a sustained response at 5 years. At the end of the treatment period, 31 patients (37%) had achieved HBeAg seroconversion. At the 5 year period, this rate rose to 60% overall. Secondary: At the end of peginterferon treatment, 27 (32%) and 55 (65%) patients had HBV DNA levels undetectable and <10,000 copies/mL, respectively. At 5 years, these rates were 13% and 31% for undetectable and <10,000 copies/mL, respectively. Only two patients (2.4%) achieved HBsAg seroclearance during the study period. At 5 years, 48 (57%) patients had normal ALT levels.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cooksley et al.[20] (2003) Peginterferon alfa-2a 90, 180 or 270 mcg/week for 24 weeks vs interferon alfa-2a 4.5 MIU TIW for 24 weeks	RCT Adult patients HbeAg-positive for >6 months	N=194 48 weeks	Primary: Loss of HBeAg after 48 weeks, suppression of HBV, ALT, and the combined response (HBeAg loss, HBV DNA suppression, and ALT normalization)	Primary: After 48 weeks, HBeAg was cleared in 37% of patients taking peginterferon 90 mcg, 35% of those taking peginterferon 180 mcg, and 29% of those taking peginterferon 270 mcg compared to 25% of patients on interferon. The difference between the 4 treatment groups was not significant (P=0.295). Suppression of HBV occurred in 43% taking peginterferon 90 mcg, 39% taking peginterferon 180 mcg, and 27% taking peginterferon 270 mcg compared to 25% of patients on interferon. The difference between the 4 treatment groups was not significant (P=0.096). The proportion of normalized ALT occurred in 43% taking peginterferon 90 mcg, 35% taking peginterferon 180 mcg, and 31% taking peginterferon 270 mcg compared to 26% of patients on interferon. The difference between the 4 treatment groups was not significant (P=0.096). The combined response (HBeAg loss, HBV DNA suppression, and ALT normalization) of all peginterferon alfa-2a doses was twice that achieved with conventional interferon alpha-2a (24% vs 12%; P=0.036). All treatment groups were similar with respect to frequency and severity of adverse events.
Hepatitis C				
Brok et al.[21] (2005) Interferon monotherapy vs interferon in combination with ribavirin	MA Patients with hepatitis C patients without HIV who received interferon monotherapy or a combination of ribavirin and interferon	N=9,991 (72 trials) Variable duration	Primary: Failure of sustained virologic response (SVR) ≥6 months and liver-related morbidity plus all-cause mortality Secondary: Failure of end-of-treatment virologic response, failure of	Primary: Compared to monotherapy, combination therapy with ribavirin significantly reduced the number with failure of SVR (RR 0.73; 95% CI, 0.71 to 0.75). For the combined total of all patients studied, combination therapy significantly reduced morbidity and mortality (OR 0.46, 95% CI: 0.22 to 0.96); however, morbidity and mortality were not significantly reduced compared to patients classified as naïve alone, nonresponders alone, or relapsers alone. Secondary: Combination therapy significantly reduced the number of patients with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			histological response, quality of life (QOL) and adverse events	failure of virologic response at end-of-treatment (RR 0.70, 95% CI: 0.67 to 0.72). Failure of histological response was significantly reduced with combination therapy, significantly reducing the number of patients with failure with grading (RR 0.84, 95% CI: 0.80 to 0.87) and staging (RR 0.95, 95% CI: 0.92 to 0.97). Where measured, combination therapy was found to significantly increase QOL, including measures of general health, social functioning and mental health. Anemia was reported in 22% of patients on combination therapy compared to 0.8% on monotherapy therapy (RR 18.22, 95% CI: 12.92 to 25.70). Rates of leukopenia were significantly higher in patients treated with combination therapy (RR 4.32, 95% CI: 1.56 to 11.90). Rates of dermatological and gastrointestinal adverse events also occurred significantly more often with combination therapy.
Chung et al.[26] (2004) Interferon alfa-2a 6 MIU TIW for 12 weeks, then 3 MIU for 36 weeks plus ribavirin vs peginterferon alfa-2a 180 mcg/week for 48 weeks plus ribavirin	RCT Adult HIV-infected patients with a confirmed diagnosis of hepatitis C not previously treated with interferon alfa	N=133 48 weeks	Primary: Virologic response at 24 weeks Secondary: Sustained virologic response (SVR) 24 weeks after treatment, virologic response at end of treatment, histologic response and changes in HIV control	Primary: At 24 weeks, 44% of patients on peginterferon had a virologic response compared to 15% on interferon (P<0.001). Secondary: SVR 24 weeks after treatment was reported in 27% of patients on peginterferon compared to 12% on interferon (P<0.03). At the end of treatment, 41% of patients on peginterferon had a virologic response compared to 12% on interferon (P<0.001). In patients without a virologic response, histologic response was reported in 35% of patients on peginterferon and 36% on interferon. CD4 cell counts increased 3.5% in patients on peginterferon and 3.0% on interferon. Rates of influenza-like symptoms, depression, and decreases in hemoglobin occurred at comparable rates between treatment groups. Eight

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients in each treatment group were withdrawn due to an adverse event or laboratory value abnormality.
Zeuzem et al.[27] (2000) Interferon alfa-2a 6 MIU TIW for 12 weeks, then 3 MIU for 36 weeks vs peginterferon alfa-2a 180 mcg/week for 48 weeks	RCT Interferon naïve adult patients with a confirmed diagnosis of hepatitis C	N=531 72 weeks	Primary: Virologic response and ALT normalization at 72 weeks	Primary: At 72 weeks, 39% of patients on peginterferon had a virologic response compared to 19% on interferon (P=0.001). At 72 weeks, sustained normalization of ALT occurred in 45% of patients on peginterferon compared to 25% on interferon (P=0.001). The frequency and severity of drug-related adverse events were comparable between treatment groups. Depression occurred in 16% of those on peginterferon and 23% of those on interferon. Psychiatric disorders were reported in 6 patients on peginterferon and 4 of those on interferon.
Rasenack et al.[28] (2003) Interferon alfa-2a 6 MIU TIW for 12 weeks then 3 MIU for 36 weeks vs peginterferon alfa-2a 180 mcg/week for 48 weeks	RCT Interferon naïve adult patients with a confirmed diagnosis of hepatitis C	N=531 24 weeks	Primary: Quality of life measured by 36–item Short-Form Health Survey (SF-36) and fatigue measured by the 10-item Fatigue Severity Scale (FSS)	Primary: At weeks 2 and 12, a significantly higher quality of life score was observed with peginterferon compared to interferon (P<0.05). No significant difference was observed at weeks 24 or 48 between treatment groups. At weeks 2, 12, and 24, significantly less disabling fatigue was observed with peginterferon compared to interferon (P<0.01). No significant difference was observed at week 48 between treatment groups.
Nevens et al.[37] (2010) Interferon alfa-2a 6 MIU TIW for 8 weeks, then 3 MIU TIW plus ribavirin	MC, OL, RCT Adult patients with chronic hepatitis C	N=443 24-48 weeks	Primary: Sustained virologic response (SVR) rate as assessed by PCR 24 weeks after treatment	Primary: After 24 weeks, SVR rates were significantly greater in the peginterferon group compared to the interferon group (52% vs 27%, P<0.001). Secondary: Sustained biochemical response rates were significantly greater in the peginterferon group compared to the interferon group (53% vs 34%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs peginterferon alfa-2a 180 mcg/week plus ribavirin			Secondary: Sustained biochemical response rate (abnormal ALT) at 24 weeks after treatment; proportion of patients with undetectable HCV RNA at weeks 12, 24, and 48	P<0.001). In respect to undetectable HCV RNA levels at weeks 12, 24, and 48, the peginterferon group had rates of 70%, 84%, and 87%, while the interferon group had rates of 42%, 52%, and 73%, respectively. A total of 190 patients (42.8%) discontinued therapy prematurely due to a lack of efficacy, adverse events, personal reasons, and lack of follow-up data. In the patients who did continue therapy, hematologic abnormalities were the most common adverse events with rates of anemia (29.7% vs 19.8%), thrombocytopenia (23.1% vs <10%), leucopenia (21.8% vs 10.4%) and neutropenia (18.3% vs <10%) for the peginterferon group compared to the interferon group.
McHutchison et al.[22] (1998) Interferon alfa-2b 3 MIU TIW for 24-48 weeks vs interferon alfa-2b 3 MIU TIW plus ribavirin 1,000-1,200 mg QD for 24 or 48 weeks	DB, PC, RCT Adult patients with hepatitis C	N=912 24-48 weeks	Primary: Sustained virologic response (SVR) 24 weeks after treatment Secondary: ALT and histologic improvement	Primary: SVR was significantly higher for all those on combination therapy (31% to 38%) compared to those receiving interferon alone (6% to 13%; P<0.001). Secondary: ALT levels normalized at the end of treatment in 58% to 65% of patients on combination therapy compared to 24% to 28% on monotherapy. Histologic improvement was significantly higher in patients on combination therapy (57% to 61%) compared to those on monotherapy (41% to 44%). Anemia necessitating a reduction in ribavirin dose occurred in 8% of patients on combination therapy. Dyspnea, pharyngitis, pruritus, rash, nausea, insomnia, and anorexia were more common with combination therapy than monotherapy. Dose reductions due to an adverse event occurred in 13% to 17% of patients on combination therapy compared to 9% to 12% in monotherapy.
Enriquez et al.[23] (2000) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000-	RCT Adult patients with hepatitis C who had previously received one or more courses	N=120 24-48 weeks	Primary: Virologic response at end of treatment and Sustained virological response (SVR) at	Primary: Virologic response at the end of therapy was 44.8% in those treated for 24 weeks and 46.8% in those treated for 48 weeks (P=0.85). SVR at 6 months was significantly higher in those treated for 48 weeks (37.1% vs 15.5%; P=0.013).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1,200 mg QD for 24 weeks vs interferon alfa-2b 3 MIU TIW plus ribavirin 1,000-1,200 mg QD for 48 weeks	of interferon alfa without achieving a sustained response		6 months after treatment	Dose adjustments due to decreased hemoglobin levels occurred in 5% of patients treated for 48 weeks and 3% in those treated for 24 weeks. Influenza-like symptoms were reported in most patients for both treatment groups during the first 2-4 weeks.
Poynard et al.[25] (1998) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000-1,200 mg QD for 24 weeks vs interferon alfa-2b 3 MIU TIW plus ribavirin 1,000-1,200 mg QD for 48 weeks vs interferon alfa-2b 3 MIU TIW plus placebo for 48 weeks	MC, PC, RCT, Adult patients with compensated hepatitis C not previously treated	N=832 48 weeks	Primary: Sustained virologic response (SVR) at week 24 after treatment Secondary: ALT and histological improvement	Primary: SVR was significantly higher for both combination regimens compared to monotherapy (P<0.001). SVR was observed in 43% of combination therapy patients treated for 48 weeks and in 35% of those treated for 24 weeks compared to 19% with SVR among those treated with monotherapy. Secondary: ALT normalization was significantly higher with combination therapy patients treated for 48 weeks (50%) compared to those treated for 24 weeks (39%; P=0.02) and those on monotherapy (24%; P<0.001). Inflammation improvement was significantly higher in patients on 48 weeks of combination therapy (63%) compared to those on 24 weeks therapy (52%; P=0.05) and monotherapy (39%; P<0.001). Those on 24 weeks of combination therapy had significantly greater improvement in inflammation compared to monotherapy (52% vs 39%; P=0.007). Significantly more patients treated for 48 weeks (monotherapy and combination therapy) discontinued therapy due to an adverse reaction, compared to those treated for 24 weeks.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sjogren et al.[24] (2005) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000 mg day vs interferon alfacon-1 15 mcg TIW plus ribavirin 1,000 mg/day	RCT Adult patients with chronic hepatitis C	N=128 48 weeks	Primary: Sustained virologic response (SVR) at 24 weeks after treatment Secondary: Virologic response based on baseline viral load and response of those with genotype 1	Primary: Twenty-four weeks after treatment, 57% of patients on interferon alfacon-1 had SVR compared to 40% on interferon alfa-2b (P=0.052). Secondary: In patients with a high viral load, a virologic response was observed in 57% of patients on interferon alfacon-1 compared to 31% on interferon alfa-2b (P=0.025). In patients with genotype 1, a response was observed in 46% of patients on interferon alfacon-1 compared to 14% on interferon alfa-2b (P=0.019). Drug-related adverse events were comparable between treatment groups.
Manns et al.[29] (2001) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000-1,200 mg daily vs peginterferon alfa-2a 1.5 mcg/kg/week plus ribavirin 800 mg daily vs peginterferon alfa-2a 1.5 mcg/kg/week for 4 weeks, then 0.5 mcg/kg/week plus	RCT Adult patients with a confirmed diagnosis of hepatitis C not previously treated	N=1,530 48 weeks	Primary: Sustained virologic response (SVR) Secondary: SVR for genotype 1, 2, and 3	Primary: SVR rates were significantly higher for the high-dose peginterferon regimen (54%) compared to low-dose peginterferon (47%; P=0.01) and interferon (47%; P=0.01). Secondary: The SVR rate for genotype 1 was 42% for the high-dose peginterferon regimen compared to 34% for low-dose peginterferon and 33% for interferon (P=0.02 vs high-dose peginterferon). The SVR rates for genotype 2 and 3 were approximately 80% for all treatment groups. The side-effect profiles were comparable among treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ribavirin 1,000-1,200 mg daily				
Carrat et al.[30] (2004) Interferon alfa-2b 3 MIU TIW plus ribavirin 800 mg daily for 48 weeks vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800 mg daily for 48 weeks	RCT Adult HIV-infected patients with a confirmed diagnosis of hepatitis C not previously treated with interferon alfa	N=412 72 weeks	Primary: Sustained virologic response (SVR) at week 72 Secondary: Histological improvement, as measured by Metavir score and Ishak grade	Primary: SVR rates were significantly higher for the peginterferon regimen (27%) compared to interferon (20%; P=0.01). Secondary: Metavir scores decreased significantly with the peginterferon regimen (-0.19) compared to interferon (0.01; P=0.02). Mean changes in Ishak score were –0.57 for peginterferon and –0.26 with interferon (P=0.24). Doses of peginterferon were modified in 16% of patients due to clinical adverse events compared to 7% with interferon (P=0.004). Dose adjustments due to laboratory abnormalities occurred in 20% of patients on peginterferon and 7% with interferon (P=0.004). Treatment discontinuation due to an adverse event was comparable between treatment groups.
Lindsay et al.[31] (2001) Interferon alfa-2b 3 MIU TIW vs peginterferon alfa-2b 0.5, 1.0 or 1.5 mcg/kg/week	RCT Adult patients with hepatitis C and compensated liver disease not previously treated	N=1,219 48 weeks	Primary: Sustained virological response (SVR) 24 weeks after completion of therapy Secondary: Normalization of ALT and improvement of liver histology	Primary: For all three doses of peginterferon, SVR was significantly higher (P≤0.042) compared to interferon therapy. Secondary: At the end of therapy, normal ALT values were significantly higher for the 1 mcg/kg (31%; P=0.002) and 1.5 mcg/kg (33%; P<0.001) peginterferon groups compared to 20% with interferon. There were no significant differences in the 0.5 mcg/kg peginterferon group and interferon. All three doses of peginterferon decreased liver inflammation to a greater extent compared to interferon therapy. The incidence and severity of adverse events were similar between treatment groups. Peginterferon regimens did demonstrate a higher incidence of injection site reactions.
Fried et al.[32] (2002) Interferon alfa-2b	RCT Adult patients with a confirmed	N=1,121 48 weeks	Primary: Sustained virologic response (SVR) at 24 weeks after	Primary: SVR rates 24 weeks after therapy were significantly higher for the peginterferon combination regimen (56%) compared to the interferon combination regimen (44%; P<0.001) and peginterferon monotherapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
3 MIU TIW plus ribavirin 1,000-1,200 mg daily vs peginterferon alfa-2a 180 mcg/week vs peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg/day	diagnosis of hepatitis C not previously treated with interferon alfa		therapy Secondary: Virologic response at end of therapy and virologic response for genotype 1, 2, and 3	regimen (29% P<0.001). Secondary: Virologic response rates at end of therapy were significantly higher for the peginterferon combination regimen (69%) compared to interferon (52%; P<0.001) and peginterferon monotherapy (59% P=0.01). SVR rates for genotype 1 were significantly higher for the peginterferon combination regimen (46%) compared to interferon (36%; P=0.01) and peginterferon monotherapy (21%; P<0.001). SVR rates for genotype 2 or 3 were significantly higher for the peginterferon combination regimen (76%) compared to interferon (61%; P=0.005) and peginterferon monotherapy (45%). Withdrawals due to adverse events were comparable between treatment groups. The most common reason for discontinuation was a psychiatric disorder. Both peginterferon regimens had a lower incidence of influenza-like symptoms and depression compared to interferon (P<0.05).
Swain et al.[38] (2010) Peginterferon alfa-2a 90-270 mcg/week plus ribavirin 800-1,600 mg/day	9 RCTs (Pooled analysis) Patients with chronic hepatitis C	N=3,460 Variable duration	Primary: Percentage of patients with significant clinical events (death, liver transplant, decompensated liver disease, encephalopathy or ascites, hepatic malignancy); undetectable HCV RNA (<50 IU/mL) at last assessment in the primary trial	Primary: A total of 1.2% of patients reported a major clinical event during the follow-up period. The most common reported events were ascites, encephalopathy, and hepatic malignancy. A total of 89.1% of patients had undetectable HCV RNA at the last visit of their primary study and at least one HCV RNA assessment in the long-term follow-up period of the study. Of these patients, 98.7% continued to have an undetectable HCV RNA at a mean of 4 years after the end of their primary study. The main findings of this study showed that patients treated with peginterferon alfa-2a plus ribavirin do not require frequent follow-up laboratory assessment of their HCV RNA status.
Lam et al.[54] (2010)	OL, MC, RCT Treatment-naïve	N=60 24 to 48 weeks	Primary: Sustained virological	Primary: At the end of the treatment period, there was no significant difference between the patients randomized to either 24 or 48 weeks of peginterferon

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Peginterferon alfa-2a 180 mcg/week plus ribavirin 800-1,200 mg daily for 24 weeks vs peginterferon alfa-2a 180 mcg/week plus ribavirin 800-1,200 mg daily for 48 weeks	adults with chronic hepatitis C genotype 6		response (SVR) at the end of treatment period Secondary: Rapid virologic response (RVR), complete early virologic response (EVR), end of treatment response(ETR), biochemical response, and treatment adherence	for sustained virologic response (70% for 24 weeks vs 79% for 48 weeks, P=0.48). Secondary: Of the subgroup of patients who had HCV RNA PCR testing at week 4 of therapy, 85% in the 24 week group and 63% in the 48 week group achieved RVR (P=0.12). RVR was a significant predictor of SVR in the 48-week group and trending towards significance in the 24-week group: 82% and 83% of those with RVR achieved SVR compared to 33% and 29% for the 24-week and 48-week groups, respectively (P=0.07 and P=0.02). A similar percentage of patients in both the 24-week and 48-week groups achieved complete EVR (96% versus 97%, P=0.90) and ETR (89% versus 94%, P=0.48). Normalization of serum ALT levels 6 months after therapy was lower in the 24-week group compared to the 48-week group (78% versus 91%; P=0.16). Treatment adherence was 63% in the 24-week group compared to 79% for the 48-week group (P=0.18). There were no differences between the two treatment groups for rates of adverse events.
Ferenci et al.[45] (2010) Peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg/day for 48 weeks (group A)	RCT, MC Adult patients with chronic hepatitis C genotype 1/4 who had early virologic response (undetectable HCV RNA at 24 weeks)	N=517 24 weeks posttreatment	Primary: Relapse and sustained virologic response (SVR; defined as an undetectable HCV RNA at the end of the 24 week follow-up)	Primary: The relapse rate was 33.6% in group A and 18.5% in group B (P=0.0115). The SVR rate was 51.1% in group A and 58.6% in group B (P>0.1). The overall SVR rate was 50.4%, including 115 of 150 patients with an RVR treated for 24 weeks and 4 of 78 patients without an EVR. There was no significant difference for rates of adverse events between the two treatment groups. Overall, there was a 17.3% adverse event rate in the 48 week group and 22.7% adverse event rate in the 72 week group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg/day for 72 weeks (group B)				
Di Bisceglie et al.[51] (2007) Peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg/day for 12 weeks vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 1,000-1,200 mg/day for 12 weeks	OL, RCT Treatment-naïve adult patients with chronic hepatitis C genotype 1	N=341 12 weeks	Primary: Change in HCV-RNA concentration at week 12 Secondary: Incidence of adverse events	Primary: At the end of week 12, there was no significant difference between the two treatment groups for change in HCV-RNA concentration. There was also no significant difference at weeks 4 and 8. Secondary: There was no significant difference between the two treatment groups for rates of adverse events. However, there was an increase in the relative frequency of chills, fever, influenza-like illness, decreased appetite, rash, vomiting, and injection site reactions in the peginterferon alfa-2b group.
Escudero et al.[50] (2008) Peginterferon alfa-2a 180 mcg/week plus ribavirin 800-1,200 mg/day	OL Treatment-naïve adult patients with chronic hepatitis C	N=183 24 weeks posttreatment	Primary: Sustained virological response (SVR; defined by undetectable HCV RNA at week 72) Secondary:	Primary: There was no significant difference between the two treatment groups for SVR (65.9% for PEG-INF alfa-2a group vs 62% for PEG-INF alfa-2b group, P=0.64). There were no differences in the percentage of patients with sustained virological response according to HCV genotype. In the subset of patients with HCV genotype 1, 50.8% of those treated with PEG-IFN alfa-2a plus ribavirin achieved sustained virological response compared with 46.6% for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,200 mg/day The duration of treatment was 24 weeks for patients with HCV genotypes 2 or 3, and 48 weeks for those with HCV genotypes 1 or 4.			Rapid virological response at 4 weeks, early virological response at 12 weeks, transient virological response, adverse events	PEG-IFN alfa-2b plus ribavirin (P=0.713). The corresponding figures for HCV genotype 2/3 were 95% versus 89.3% (P=0.63) and for genotype 4 were 91.7% versus 83.3% (P=1.0). Other efficacy variables including rapid virological response at 4 weeks, early virological response at 12 weeks and transient virological response were also similar among patients in both treatment groups. There were similar rates of adverse events in both treatment groups as well as discontinuation of study drug due to adverse events (22 patients alfa-2a group vs 28 patients alfa-2b group, P=NS).
Scotto et al.[49] (2008) Peginterferon alfa-2a 180 mcg/week plus ribavirin 15 mg/kg/day for 48 weeks vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 15 mg/kg/day for 48 weeks	OL, RCT Adult patients with chronic hepatitis C who were unresponsive to previous combined therapy (standard interferon alfa plus ribavirin for ≥3 months)	N=108 24 weeks posttreatment	Primary: Sustained virological response (SVR; defined by undetectable serum HCV RNA at 72 weeks) Secondary: Sustained biochemical response, adverse events	Primary: At the end of the 72-week period, there was no difference between the two treatment groups for SVR (20.4% for PEG-INF alfa-2a vs 18.5% for PEG-INF alfa-2b, P=NS). Secondary: There was no difference in normalization of ALT levels at the end of the 72-week period (22.2% PEG-INF alfa-2a group vs 24.1% PEG-INF alfa-2b group, P=NS). In terms of adverse events, there was no difference between the two groups.
Rumi et al.[52] (2010)	OL, RCT Treatment-naïve	N=431 24 weeks	Primary: Sustained virological	Primary: The overall SVR rate was higher in PEG-IFN alfa-2a group than in PEG-INF alfa-2b group (66% vs 54%, respectively, P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg/day for 24-48 weeks (depending on genotype) vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,200 mg/day for 24-48 weeks (depending on genotype)	adult patients with chronic hepatitis C	posttreatment	response (SVR; undetectable HCV-RNA 24 weeks after treatment), adverse events	In patients with genotype 1 and 4, the SVR rates were 48% and 32% with PEG-IFN alfa-2a and PEG-IFN alfa-2b, respectively (P=0.04). In patients with genotype 2, the SVR rates were 96% and 82% with PEG-IFN alfa-2a and PEG-IFN alfa-2b, respectively (P=0.01). Rates of adverse events were similar between the two treatment groups. Eighteen patients in the peginterferon alfa-2a group compared to 23 in the alfa-2b group discontinued therapy due to adverse events.
Ascione et al.[44] (2010) Peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg/day for 48 weeks (genotype 1 or 4) or 24 weeks (genotype 2 or 3) (group A) vs peginterferon alfa-2b 1.5	RCT, OL Treatment-naïve adult patients with chronic hepatitis C	N=320 24 weeks posttreatment	Primary: Sustained virologic response (SVR) after 24 weeks of untreated follow-up	Primary: SVR was achieved in 68.8% of patients treated with peginterferon alfa-2a compared to 54.4% of patients treated with peginterferon alfa-2b (P=0.008). Higher SVR rates were obtained in group A than group B among patients with genotype 1/4 (54.8% vs 39.8%; P=0.04), with genotype 2/3 (88.1% vs 74.6%; P=0.046), without cirrhosis (75.6% vs 55.9%; P=0.005), and with baseline levels HCV RNA >500,000 IU/mL (69% vs 46.2%; P=0.002). SVR rates in groups A and B were not statistically different among patients with baseline HCV RNA ≤500,000 IU/mL ([68.4% vs 65.7%; P=0.727) or in patients with cirrhosis (42.4% vs 46.1%; P=0.774).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg/kg/week plus ribavirin 1,000-1,200 mg/day for 48 weeks (genotype 1 or 4) or 24 weeks (genotype 2 or 3) (group B)				
Kamal et al.[48] (2011) Peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg daily for 48 weeks vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 1,000-1,200 mg/day for 48 weeks	OL, RCT Treatment-naïve adult patients with chronic hepatitis C genotype 4	N=213 24 weeks posttreatment	Primary: Sustained virological response (SVR) defined by undetectable HCV RNA 24 weeks after treatment Secondary: Biochemical response, histological response, quality of life, adverse events, adherence	Primary: Significantly more patients in the PEG-INF alfa-2a group had achieved SVR at the end of the study period compared to the PEG-INF alfa-2b group (70.6% PEG-INF alfa-2a vs 54.6% PEG-INF alfa-2b; P=0.0172). Significantly more patients in the PEG-INF alfa-2b group had relapse compared to the PEG-INF alfa-2a group (15.7% vs 5.1%; P=0.0019). Secondary: Among patients treated with PEG-IFN alfa-2a and ribavirin, 41.3% had undetectable HCV RNA after 4 weeks of therapy (RVR) compared with 27.78% of patients treated with PEG-IFN alfa-2b and ribavirin (P=0.0456). Among those who did not achieve RVR, 46.9% and 26.9% of patients in PEG-IFN alfa-2a and PEG-IFN alfa-2b groups, respectively, had undetectable HCV RNA at week 12 (P=0.1213). A total of 39.1% and 30.8% of patients in PEG-IFN alfa-2a and PEG-IFN alfa-2b groups, respectively, had a >2 $\log_{10}$ decline in HCV RNA (P=0.3754). Significantly more patients with RVR went on to achieve an SVR compared with their counterparts who lacked that response (97.3% vs 2.7%; P<0.0001). The mean time duration to aviremia was longer among patients receiving PEG-IFN alfa-2b than PEG-IFN alfa-2a (P=0.0283).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Follow-up biopsies, performed on 42 patients showed that the rates of improvement in liver steatosis, liver grading scores and fibrosis scores at the end of the study period did not differ significantly between groups (P>0.05). The SF-36v2 and CLDQ were low during therapy and improved significantly after therapy successful therapy. Overall, there was no significant difference between the two groups for rates of adverse events.
Brixner et al.[47] (2009) Peginterferon alfa-2a plus ribavirin (2a group) vs peginterferon alfa-2b plus ribavirin (2b group)	RETRO Adult patients with chronic hepatitis C	N=1783 Variable duration	Primary: Treatment persistence (duration of prescriptions filled after index date)	Primary: There was no significant difference in persistence rates for patients in the 2a group compared to the 2b group (median time to discontinuation: 245 days vs 226 days, respectively; P=0.072).
Witthoeft et al.[41] (2010) Peginterferon alfa-2a plus ribavirin (group A) vs peginterferon alfa-2b plus ribavirin (group B)	RETRO Adult patients with chronic hepatitis C	N=3470 24 weeks	Primary: Early virologic response (≥2 $\log^{10}$ drop in HCV RNA or HCV RNA ≤50 IU/mL after 12 weeks), end of treatment response (EOT) and sustained virological response (SVR; HCV RNA ≤50	Primary: There was no significant difference in any of the virological response parameters measured between group A and group B. Overall, significantly fewer patients in group A discontinued therapy prior to the end of treatment compared to those in group B (21.8% vs 29.6%, P≤0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dosing was up to discretion of treating physician.			IU/mL or HCV RNA undetectable after 24 weeks)	
Van Vlierberghe et al.[40] (2010) Peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,200 mg/day for 48 weeks	OL, OBS Treatment-naïve adult patients with chronic hepatitis C	N=219 48 weeks	Primary: Sustained virological response (SVR) defined by undetectable HCV RNA 6 months after treatment completion	Primary: A total of 49.3% of patients had an undetectable HCV RNA at the end of 48 weeks of therapy. However, there was a fairly significant dropout rate and loss to follow-up (98 patients; 44.7%). A total of 41 patients discontinued therapy at various time points due to adverse events (n=23) or serious adverse events (n=18). The most common serious adverse events were anemia, fatigue/asthenia/malaise, and fever.
Bruix et al.[43] (2011) Peginterferon alfa-2b 0.5 mcg/kg/week vs no treatment	OL, RCT Adult patients with chronic hepatitis C who had failed previous interferon alfa plus ribavirin therapy	N=626 5 years	Primary: Time to development of first clinical event of liver decompensation, development of HCC, death, or liver transplantation	Primary: There was no significant difference between the treatment groups for time to first clinical event (11% vs 9%for peginterferon and no treatment groups, respectively; P=0.144). There were significantly more adverse events in the treatment group compared to the no treatment group. Additionally, significantly more patients discontinued therapy in the treatment group compared to the no treatment group.
Buti et al.[53] (2010) Peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,400 mg/day for 48 weeks (group A) vs peginterferon	OL, MC, RCT Adult patients with chronic hepatitis C genotype 1	N=1,428 48 to 72 weeks	Primary: Sustained virological response (SVR) at then end of the treatment period Secondary: End-of-treatment virologic response, relapse rates, adverse events	Primary: At the end of the treatment period, there was no difference in the rates of SVR between the two treatment groups (43% vs 48%, P=0.644). Secondary: End-of-treatment response was 83% and 70% in groups A and B, respectively. Relapse rates were similar in slow responders treated for 48 or 72 weeks (47% versus 33%, P=0.169). There was no significant difference between the two groups when comparing adverse events; however the raw rates of adverse events in the group receiving 72 weeks of treatment were higher and may represent a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,400 mg/day for 72 weeks (group B)				clinical significance (3.5% vs 8.2%).
Brady et al.[42] (2010) Peginterferon alfa-2b 3.0 mcg/kg/week for 12 weeks, then 1.5 mcg/kg/week for 36 weeks, plus ribavirin 11-15 mg/kg/day for 48 weeks (induction group) vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 11-15 mg/kg/day for 48 weeks (SOC)	RCT, OL Treatment-naïve adult patients with chronic hepatitis C genotype 1 or 4	N=610 6 months	Primary: Sustained virologic response (SVR) defined as persistent loss of HCV RNA at 6 months of follow-up evaluation after completion of 48 weeks of treatment = week 72) Secondary: Early virologic response (virus-negative at week 12); subgroup analysis of SVR response in African American and Hispanic populations	Primary: Complete early virologic response was 62.6% versus 57.7% in induction versus SOC (P=NS). Overall SVR was 32% in the induction group versus 29% in SOC group (P=0.434). Secondary: A total of 48.8% of patients from the induction group and 42.8% of patients from the SOC group discontinued therapy before 48 weeks (P=0.2). Overall SVR in African Americans was similar in the patients receiving induction therapy (35%) versus SOC (32%; P=0.9). Overall SVR for Hispanic patients was similar in patients receiving induction therapy (36.1%) versus SOC (22.5%; P=0.292). As shown in other studies with peginterferon alfa-2b combined with ribavirin, there was a large portion of patients experience adverse events. There were no significant life-threatening adverse events reported in any study group. There were also no significant differences between the two study groups for rates of adverse events.
McHutchison et al.[19] (2009) Peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800 to	RCT, DB, MC Patients ≥18 years of age with compensated liver disease due to chronic HCV genotype 1 infection	N=3,070 24 weeks posttreatment	Primary: Sustained virologic response (defined as undetectable HCV RNA levels 24 weeks after the completion of therapy)	Primary: The rates of sustained virologic response did not differ significantly among the three treatment groups, with a rate of 39.8% (95% CI, 36.8 to 42.8) for standard-dose peginterferon alfa-2b, 38.0% (95% CI, 35.0 to 41.0) for low-dose peginterferon alfa-2b, and 40.9% (95% CI, 37.9 to 43.9%) for peginterferon alfa-2a, (P=0.20 for standard-dose vs low-dose peginterferon alfa-2b; P=0.57 for standard-dose peginterferon alfa-2b vs peginterferon alfa-2a).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1,400 mg/day for 48 weeks (standard-dose arm) vs peginterferon alfa-2b 1.0 mcg/kg/week plus ribavirin 800 to 1,400 mg/day for 48 weeks (low-dose arm) vs peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000 to 1,200 mg/day for 48 weeks	and a detectable plasma HCV RNA level who had not been previously treated for hepatitis C infection		Secondary: Rates of virologic response during the treatment phase and relapse (defined as an undetectable HCV RNA level at the end of the treatment phase, with a detectable HCV RNA level during the follow-up period)	Secondary: Response rates at the end of the treatment phase were higher with peginterferon alfa-2a than with either peginterferon alfa-2b regimen, however the virologic relapse rate was also higher. HCV RNA suppression at treatment weeks 4 and 12 was strongly associated with achievement of sustained virologic response in all 3 treatment groups. Fewer than 5% of patients who had a reduction from the baseline HCV RNA level of less than 1 $\log_{10}$ IU/ml at week 4 also had a sustained virologic response. A prolonged time (>12 weeks of therapy) to undetectable HCV RNA level was associated with a higher likelihood of relapse after treatment. Rates of sustained virologic response were similar among the three treatment groups, within the subgroups of patients receiving the same dose of ribavirin. Relapse rates were 23.5% for standard-dose peginterferon alfa-2b, 20.0% for low-dose peginterferon alfa-2b, and 31.5% for peginterferon alfa-2a (95% CI, –13.2 to –2.8 for the standard dose regimens; 95% CI, –1.6% to 8.6% for standard-dose peginterferon alfa-2b vs low-dose peginterferon alfa-2b). The types and frequencies of adverse events were similar among the three groups. The most common adverse events included influenza- like symptoms, depression, and the hematologic events of anemia and neutropenia. The proportion of patients with neutropenia was 21.1% in patients receiving peginterferon alfa-2a, 19.4% in patients receiving standard-dose peginterferon alfa-2b, and 12.5% in patients receiving low-dose peginterferon alfa-2b. Most psychiatric adverse events were mild or moderate and were not treatment-limiting.
Hairy Cell Leukemia				
Grever et al.[33] (1995) Interferon alfa-2a	RCT Patients diagnosed with hairy cell	N=313 Mean 57 months	Primary: Rates of complete and partial to complete remission	Primary: Complete and partial remission was significantly higher with pentostatin compared to interferon (P<0.05). Complete remission was achieved in 11% on interferon compared to 76% on pentostatin. Partial-to-complete

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
3 MIU TIW vs pentostatin 4 mg/m^2 intravenously every 2 weeks	leukemia that were previously untreated for this condition			remission was achieved in 38% of patients on interferon compared to 79% in patients on pentostatin. Myelosuppression was significantly more frequent with pentostatin (P=0.013).
Federico et al.[34] (1994) Interferon alfa (either alfa-2a, alfa-2b or alfa-n1*) 3 MIU daily Patients with a partial response may be randomly selected to undergo splenectomy.	RCT Adult patients with histologically confirmed hairy cell leukemia not previously treated.	N=177 38 months	Primary: Rates of remission (complete, partial or minor), overall response rate (complete, partial and minor remission) Secondary: Survival after splenectomy	Primary: Treatment with interferon alfa resulted in complete remission in 16.9%, partial remission in 62.0% and minor remission in 16%. Response rate was 92.7% for interferon alfa-2a, 97.2% for interferon alfa-2b and 95.3% for interferon alfa-n1. Secondary: Four-year progression-free survival for patients that had undergone a splenectomy after a partial response on interferon was 53%, compared to 22% of patients assigned to observation (P=0.116).

Drug regimen abbreviations: MIU=million international units, QD=once daily, TIW= three times weekly
Study abbreviations: CI=confidence interval, DB=double-blind, FSS=fatigue severity scale, MA=meta-analysis, MC=multicenter, PC=placebo-controlled, QOL=quality of life, RCT=randomized controlled trial, RR=relative risk, SF-36=Short-Form Health Survey
Other abbreviations: ALT=alanine aminotransferase, HBeAg=hepatitis B e antigen, HBV=hepatitis B virus, HIV=human immunodeficiency virus, SVR=sustained virologic response
*Not commercially available in the US

Additional Evidence

Dose Simplification
Several trials have determined that longer treatment durations with combination interferon therapy (48 weeks) are more effective than shorter treatment regimens (24 weeks).[23,25] Bernstein et al. conducted a meta-analysis of three trials comparing peginterferon alfa-2a and interferon alfa-2a to measure the impact of interferon therapy on quality of life and treatment adherence in patients with hepatitis C.[35] Peginterferon was found to provide a significantly higher sustained virologic response, and was associated with an improvement in quality of life and less fatigue (P<0.01).

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

Impact on Physician Visits
Perrillo et al. evaluated the effects of interferon treatment on quality of life and health care utilization in patients with hepatitis C.[36] Patients received treatment interferon alfa-2b three times weekly or peginterferon alfa-2a once weekly. After 24 and 48 weeks, patients receiving peginterferon experienced significantly less impairment of quality of life compared to patients receiving interferon (P<0.05). Fewer patients treated with peginterferon required prescription medications to treat adverse events related to HCV therapy as compared to interferon therapy (56.9% vs 70.2%, respectively; P=0.007). There were no significant differences between the treatment groups in other areas of healthcare resource utilization.

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 Interferons

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Interferon alfa-2b	injection	Intron® A	$$$$$	N/A
Interferon alfacon-1	injection	Infergen®	$$$$$	N/A
Interferon alfa-n3	injection	Alferon N®	$$$$$	N/A
Peginterferon alfa-2a	injection	Pegasys®	$$$$$	N/A
Peginterferon alfa-2b	injection	PegIntron®	$$$$$	N/A

N/A=Not available

X. Conclusions

Interferons are naturally occurring proteins with antiviral, antiproliferative and immunoregulatory properties.[1-7] The FDA-approved indications vary among the products; however, the interferons are primarily used for the treatment of chronic hepatitis B and chronic hepatitis C. None of the interferons are available in a generic formulation.

Guidelines recommend the use of peginterferon alfa as one of several initial treatment options for patients with chronic hepatitis B.[14,18] Interferon alfa-2a and peginterferon alfa-2a were shown to be equally effective following 48 weeks of treatment.[20]

For the treatment of chronic hepatitis C, guidelines recommend the use of peginterferon alfa in combination with ribavirin.[14-17] They do not give preference to one pegylated product over another. The peginterferon alfa products have both been shown to be more effective than standard interferon alfa products for the treatment of chronic hepatitis C.[26-27,29-32,37] Studies directly comparing the peginterferon alfa products have demonstrated mixed results.[19,44,48,50-52] The largest trial was conducted by McHutchison et al. and included over 3,000 patients with chronic hepatitis C genotype 1 infection. The investigators demonstrated similar sustained virologic response rates, relapse rates and adverse events with peginterferon alfa-2a and peginterferon alfa-2b.[19]

Interferon alfa-2b and interferon alfa-n3 are approved for the treatment of condylomata acuminata. However, the interferons are considered a second-line treatment option by the CDC and there are no published clinical trials which directly compare these agents.[15] Interferon alfa-2b is also approved for the treatment of selected patients with AIDS-related Kaposi's sarcoma, hairy cell leukemia, follicular Non-Hodgkin's lymphoma, and as an adjuvant to surgical treatment in patients with malignant melanoma. Due to the limited usage anticipated for most of these indications, the interferon alfa products should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand interferon alfa 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. Peginterferon alfa-2a (Pegasys®) and peginterferon alfa-2b (PegIntron®) offer significant clinical advantages in general use over the other brands, generics and OTC products in the same class (if applicable), but are comparable to each other.

XI. Recommendations

No brand interferon alfa 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.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand peginterferon alfa product is selected as a preferred agent.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Neuraminidase Inhibitors
AHFS Class 081828
May 9, 2012

I. Overview

Influenza A viruses (primarily H1N1 and H3N2) and influenza B viruses circulate worldwide. Influenza epidemics occur nearly every year making this disease a major cause of respiratory illness in the United States.[6] The majority of complications, hospitalizations and deaths from seasonal influenza occur in persons over 65 years old, children younger than 2 years old, and persons of any age with certain underlying health conditions. The most effective way to minimize the negative impact of influenza is through annual vaccination. According to the 2011 recommendations of the Advisory Committee on Immunization Practices (ACIP), annual influenza vaccination is recommended for everyone over 6 months of age.[11]

Antiviral medications are an important adjunct to vaccination for the control and prevention of influenza disease. The neuraminidase inhibitors block the viral release mechanisms during the replication cycles of influenza A and B.[1-3] Neuraminidase is an enzyme that is necessary for release of daughter virions from infected cells. Without the action of neuraminidase, the new virions are tethered to the cellular membrane glycoproteins of their parent cells and therefore, the virus will remain aggregated at the cell surface and cannot spread to other cells.[8-9] Because the peak range for influenza virus replication is 24 to 72 hours after the onset of illness, oseltamivir and zanamivir should be administered as early as possible.[1-5]

The neuraminidase inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products available. This class was last reviewed in November 2009.

Table 1. Neuraminidase Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Oseltamivir	capsule, suspension	Tamiflu®	Tamiflu®†
Zanamivir	powder for inhalation	Relenza®	Relenza®†

†The preferred status of this product is contingent upon statewide influenza epidemiology status as reported by the CDC.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the neuraminidase inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the Neuraminidase Inhibitors

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention (CDC): **Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP)[11] (2011)**	General Considerations • During most influenza seasons, rates of serious illness and death are highest among persons aged ≥65 years, children aged <2 years, and persons of any age who have medical conditions that place them at increased risk for complications from influenza. • Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. • All persons aged ≥6 months are recommended for annual influenza vaccination. • Antiviral medications are effective for the prevention of influenza and can reduce the duration and severity of illness. • The selection of antiviral medications should be based on influenza antiviral resistance patterns, local, state, and national influenza

Clinical Guideline	Recommendation(s)

	surveillance information on influenza virus type or influenza A virus subtype, the characteristics of the person who is ill, and results of influenza testing if testing is done.
	• Empiric antiviral treatment often is required to avoid treatment delays.
	• Antiviral treatment is recommended as soon as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness or who require hospitalization.
	• Antiviral treatment also may be considered on the basis of clinical judgment for any outpatient with confirmed or suspected influenza who does not have known risk factors for severe illness if treatment can be initiated within 48 hours of illness onset.
	• Oseltamivir or zanamivir are the primary antiviral agents recommended for the prevention and treatment of influenza. Oseltamivir may be used for treatment or chemoprophylaxis of influenza among infants aged <1 year when indicated.
	• Resistance among influenza A (H3N2) virus strains has made amantadine and rimantadine less useful clinically. Circulating 2009 H1N1 virus strains are resistant to the adamantanes. Therefore, amantadine and rimantadine are not recommended for antiviral treatment or chemoprophylaxis of currently circulating influenza A virus strains.
	• Development of resistance to zanamivir or oseltamivir has also been identified during treatment of seasonal influenza. Transmission of neuraminidase-inhibitor-resistant influenza B viruses has been reported among household contacts. Sporadic cases of resistance to oseltamivir have been observed among persons with 2009 H1N1 virus infection. Emergence of oseltamivir-resistant 2009 H1N1 virus strains within 48 hours after initiation of treatment has been reported. Transmission of oseltamivir-resistant influenza B virus strains or 2009 H1N1 virus strains acquired from persons treated with oseltamivir is rare.
	<u>Treatment Indications</u>
	• Antiviral treatment is recommended as soon as possible for all persons with suspected or confirmed influenza requiring hospitalization or who have progressive, severe or complicated illness regardless of previous health or vaccination status.
	• Empiric antiviral treatment is often necessary, and providers should not delay initiation of treatment while awaiting confirmatory diagnostic tests results or if specimens are not obtained.
	• Among outpatients, antiviral treatment with a neuraminidase inhibitor is recommended for all persons with suspected or confirmed influenza who are at higher risk for influenza complications because of age or underlying medical conditions.
	• Persons at higher risk for influenza complications who are recommended for antiviral treatment for suspected or confirmed influenza include:
	  o Children aged <2 years
	  o Adults aged ≥65 years;
	  o Persons with chronic pulmonary, cardiovascular, renal, hepatic, hematological, metabolic disorders or neurologic and neurodevelopment conditions
	  o Persons with immunosuppression
	  o Women who are pregnant or postpartum
	  o Persons aged <19 years who are receiving long-term aspirin therapy
	  o American Indians/Alaska Natives
	  o Persons who are morbidly obese

Clinical Guideline	Recommendation(s)
	○ Residents of nursing homes and other chronic-care facilities • The benefits of antiviral treatment are likely to be greatest if treatment is started as soon as possible after illness onset, and evidence for benefit is strongest in studies in which treatment was started within 48 hours of illness onset. • Treatment of any person with confirmed or suspected influenza who requires hospitalization is recommended, even if the patient presents >48 hours after illness onset. • Treatment also can be considered for outpatients with uncomplicated, suspected, or confirmed influenza who are not known to be at increased risk for developing severe or complicated illness if antiviral treatment can be initiated within 48 hours of illness onset. • Persons with influenza who present with an uncomplicated febrile illness typically do not require treatment unless they are at higher risk for influenza complications, but early empiric antiviral treatment of these patients also might provide benefit (e.g., a shortened duration of illness). • Persons with influenza who are already beginning to recover do not need to start treatment. <u>Postexposure Chemoprophylaxis Indications</u> • Decisions on whether to administer antivirals for chemoprophylaxis should take into account the exposed person's risk for influenza complications, the type and duration of contact, recommendations from local or public health authorities, and clinical judgment. • Postexposure chemoprophylaxis for persons should be only used when antivirals can be started within 48 hours of the most recent exposure. • Chemoprophylaxis with antiviral medications is not a substitute for influenza vaccination when influenza vaccine is available. • Either oseltamivir or zanamivir is recommended for antiviral chemoprophylaxis of 2009 H1N1, influenza A (H3N2), or influenza B influenza virus infection. • An emphasis on early treatment is an alternative to chemoprophylaxis in managing certain persons who have had a suspected exposure to influenza virus. <u>Duration of Chemoprophylaxis</u> • Postexposure chemoprophylaxis is administered for no more than 10 days after the most recent known exposure to a close contact known to have influenza. • The duration of pre-exposure chemoprophylaxis based on potential exposure in the community depends on the duration of community influenza activity. Regimens as long as 28 days for zanamivir, and 42 days for oseltamivir, have been well tolerated, but no published data are available regarding use of regimens lasting >6 weeks. <u>Considerations for Antiviral Use if Oseltamivir-Resistant Virus Strains Are Circulating</u> • Since September 2009, almost all (99%) circulating influenza A and B viruses have been susceptible to oseltamivir. Information about antiviral treatment options has been outlined according to the results of influenza diagnostic testing. • If oseltamivir-resistant viruses are not circulating, antiviral treatment for influenza should consist of either oseltamivir or zanamivir. <u>Control of Influenza Outbreaks in Institutions</u> • Use of antiviral drugs for treatment and chemoprophylaxis of influenza is a key component of influenza outbreak control in institutions that house patients at higher risk for influenza complications.

Clinical Guideline	Recommendation(s)
	• Both adamantanes and neuraminidase inhibitors have been used successfully to control outbreaks caused by susceptible strains when antiviral medications are combined with other infection-control measures. • When chemoprophylaxis is indicated, a neuraminidase inhibitor medication should be started as early as possible to reduce the spread of the virus. • Chemoprophylaxis should be administered to all eligible residents, regardless of whether they received influenza vaccination during the previous fall, and should continue for a minimum of 2 weeks. If surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until approximately 10 days after illness onset in the last patients. • During institutional outbreaks, chemoprophylaxis also can be offered to unvaccinated staff members who provide care to persons at high risk of complications. • Chemoprophylaxis should be considered for all employees, regardless of their influenza vaccination status, if indications exist that the outbreak is caused by a strain of influenza virus that is not well matched by the vaccine.

American Academy of Pediatrics (AAP): **Recommendations for Prevention and Control of Influenza in Children, 2011-2012[10] (2011)**	<u>Annual Influenza Vaccination is Recommended for the Following Groups:</u>
	• All children, including infants born prematurely, 6 months of age and older with conditions that increase the risk of complications from influenza.
	• Household contacts and out-of-home care providers of:
	  o Children with high-risk conditions
	  o Children younger than 5 years of age
	• Health care professionals
	• All women who are pregnant, considering pregnancy, or breastfeeding during the influenza season.
	<u>Use of Antiviral Medications</u>
	• Oseltamivir and zanamivir are the only antiviral medications routinely recommended for chemoprophylaxis or treatment during the 2011–2012 season.
	• All strains of influenza currently anticipated to circulate are susceptible to neuraminidase inhibitors, but have high rates of resistance to amantadine and rimantadine.
	• Treatment should be considered for:
	  o Any child hospitalized with presumed influenza or with severe, complicated, or progressive illness, regardless of influenza immunization status.
	  o Influenza infection of any severity in children at high risk of complications of influenza infection.
	  o Any otherwise healthy child with influenza infection for whom a decrease in duration of clinical symptoms is felt to be warranted by his or her provider if treatment can be initiated within 48 hours of illness onset.
	• Earlier treatment provides more optimal clinical responses, although treatment after 48 hours of symptoms in the child with moderate-to-severe disease or with progressive disease might still provide some benefit.
	• Children <1 year of age are at increased risk of influenza-related complications. Although there are no antiviral medications licensed by the Food and Drug Administration for this age group and the 2009 H1N1 pandemic Emergency Use Authorization has expired,

Clinical Guideline	Recommendation(s)
	recommendations for use of oseltamivir in this young age group can still be followed. • Antiviral treatment should be started as soon as possible after illness onset and should not be delayed while waiting for a definitive influenza test result. Recommendations for Chemoprophylaxis During an Influenza Outbreak • For children at high risk of complications from influenza for whom influenza vaccine is contraindicated. • For children at high risk during the 2 weeks after influenza immunization. • For family members or HCP who are unimmunized and are likely to have ongoing, close exposure to: unimmunized children at high risk; or infants and toddlers who are younger than 24 months. • For control of influenza outbreaks for unimmunized staff and children in a closed institutional setting with children at high risk. • As a supplement to immunization among children at high risk, including children who are immunocompromised and might not respond to vaccine. • As postexposure prophylaxis for family members and close contacts of an infected person if those people are at high risk of complications from influenza. • Chemoprophylaxis should not be considered a substitute for immunization.

Infectious Diseases Society of America (IDSA): **Seasonal Influenza in Adults and Children— Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practice Guidelines of the Infectious Diseases Society of America[12] (2009)**	Antivirals for Treatment of Seasonal Influenza
	• Treatment is recommended for both adults and children with influenza virus infection who meet the following criteria:
	  ○ Persons with laboratory-confirmed or highly suspected influenza virus infection at high risk of developing complications within 48 h after symptom onset. Treatment is recommended regardless of influenza vaccination status and regardless of severity of illness.
	  ○ Persons requiring hospitalization for laboratory-confirmed or highly suspected influenza illness, regardless of underlying illness or influenza vaccination status, if treatment can be initiated within 48 h after onset of symptoms. However, persons who require hospitalization for laboratory-confirmed influenza whose positive laboratory test result for influenza is from a specimen obtained >48 h after the onset of illness may also benefit from treatment.
	• Treatment should be considered for both adults and children with influenza virus infection who meet the following criteria:
	  ○ Outpatients at high risk of complications with illness that is not improving and who have a positive influenza test result from a specimen obtained >48 h after onset of symptoms.
	  ○ Outpatients with laboratory-confirmed or highly suspected influenza virus infection who are not at increased risk of complications, whose onset of symptoms is >48 h before presentation, and who wish to shorten the duration of illness and further reduce their relatively low risk of complications or who are in close contact with persons at high risk of complications secondary to influenza infection. Those whose onset of symptoms occurred >48 h before presentation with persisting moderate to severe illness may also benefit from treatment, but safety and efficacy in this population have not been evaluated prospectively.

Clinical Guideline	Recommendation(s)
	• On the basis of antiviral susceptibility patterns current as of March 2009, infection with a seasonal influenza A (H1N1) virus should be treated with either zanamivir or an adamantine (preferably rimantadine because of its more favorable adverse effect profile); oseltamivir should not be used to treat infection with seasonal influenza A (H1N1). Infection with a seasonal influenza A (H3N2) virus should be treated with oseltamivir or zanamivir; the adamantanes should not be used to treat influenza A (H3N2). If subtype information is unavailable, influenza A should be treated either with zanamivir or with a combination of oseltamivir and rimantadine. Infection with an influenza B virus should be treated only with oseltamivir or zanamivir. Antivirals for Chemoprophylaxis of Seasonal Influenza • Influenza vaccination is the primary tool to prevent influenza, and antiviral chemoprophylaxis is not a substitute for influenza vaccination. When influenza viruses are circulating in the community, chemoprophylaxis can be considered for high-risk persons during the 2 weeks after vaccination before an adequate immune response to inactivated vaccine develops (6 weeks for children who were not previously vaccinated and who require 2 doses of vaccine). • Antiviral chemoprophylaxis should be considered for adults and children aged ≥1 year who are at high risk of developing complications from influenza for which influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g., persons who are significantly immunocompromised). • Antiviral chemoprophylaxis (in conjunction with prompt administration of the inactivated vaccine) should be considered for adults and children aged ≥1 year who are at high risk of developing complications from influenza virus infection and have not yet received influenza vaccine when influenza activity has already been detected in the community. • Antiviral chemoprophylaxis may be considered for unvaccinated adults, including health care workers, and for children aged ≥1 year that are in close contact with persons at high risk of developing influenza complications during periods of influenza activity. Whenever possible, influenza vaccine should be administered; 2 weeks after administration, chemoprophylaxis may be discontinued. • Antiviral chemoprophylaxis is recommended for all residents (vaccinated and unvaccinated) in institutions that are experiencing influenza outbreaks. • The strongest consideration for use of antiviral chemoprophylaxis should be given to persons at the highest risk of influenza-associated complications. • Antiviral chemoprophylaxis should be considered for persons at high-risk of developing complications from influenza if influenza vaccine is not available due to shortage. If vaccine is available, it should be administered to these persons. • Antiviral chemoprophylaxis can be considered for high-risk persons in situations in which there is documented low influenza vaccine clinical effectiveness because of the circulation of influenza virus strains that are antigenically distant from the vaccine strains, such that a substantial increase in vaccine failures is anticipated, as determined by federal, state, and local public health authorities. • In persons at high risk of complications who are not adequately protected as a result of poor immune responses (e.g., in persons who are significantly immunocompromised), lack of influenza vaccination, or ineffective vaccine (e.g., when antigenically distant strains are

Clinical Guideline	Recommendation(s)
	circulating), antiviral chemoprophylaxis should be initiated at the onset of sustained community influenza activity, as determined by local public health authorities. • Antiviral chemoprophylaxis use for appropriate persons within households should be initiated when 1 family member develops suspected or confirmed influenza and any other family member is at high risk of complications secondary to infection, including infants aged <6 months. In this setting, all noninfected family members should receive antiviral chemoprophylaxis. • If inactivated influenza vaccine is administered, antiviral chemoprophylaxis can generally be stopped 2 weeks after vaccination for persons in non-institutional settings. • When antiviral chemoprophylaxis is used in a household after the diagnosis of influenza in 1 family member, chemoprophylaxis should be continued for 10 days. • In persons at high risk of developing complications from influenza for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g., persons who are significantly immunocompromised), chemoprophylaxis should continue for the duration that influenza viruses are circulating in the community during influenza season. • On the basis of antiviral susceptibility patterns current as of March 2009, either zanamivir or an adamantane (preferably rimantadine because of its more favorable adverse effect profile) should be used for seasonal influenza A (H1N1) chemoprophylaxis; oseltamivir should not be used for seasonal influenza A (H1N1) chemoprophylaxis. Either oseltamivir or zanamivir should be used for seasonal influenza A (H3N2) chemoprophylaxis; the adamantanes should not be used for influenza A (H3N2) chemoprophylaxis. If subtype information is unavailable, either zanamivir or a combination of oseltamivir and rimantadine should be used for influenza A chemoprophylaxis. Only oseltamivir or zanamivir should be used for influenza B chemoprophylaxis.
World Health Organization (WHO) Rapid Advice Guideline Panel on Avian Influenza: **WHO Rapid Advice Guidelines for Pharmacological Management of Sporadic Human Infection with Avian Influenza A (H5N1) Virus**[14] **(2007)**	• Clinicians should administer oseltamivir treatment as soon as possible in patients with confirmed or strongly suspected H5N1 infection. • Clinicians might administer zanamivir in patients with confirmed or strongly suspected infection with H5N1 virus. • Clinicians should not administer amantadine or rimantadine alone as first-line treatment to patients with confirmed or strongly suspected human infection with H5N1 if neuraminidase inhibitors are available. • Clinicians might administer amantadine or rimantadine as a first-line treatment to patients with confirmed or strongly suspected infection with H5N1 if neuraminidase inhibitors are not available and especially if the virus is known or likely to be susceptible. • Clinicians might administer a combination of a neuraminidase inhibitor and amantadine or rimantadine to patients with confirmed or strongly suspected infection with H5N1 if neuraminidase inhibitors are available and especially if the virus is known or likely to be susceptible. • Oseltamivir or zanamivir should be administered as chemoprophylaxis continuing for 7-10 days after the last known exposure in high-risk exposure groups. • Oseltamivir or zanamivir might be administered as chemoprophylaxis continuing for 7-10 days after the last known exposure in moderate-risk exposure groups.

Clinical Guideline	Recommendation(s)
	• Oseltamivir or zanamivir should probably not be administered as chemoprophylaxis in low-risk exposure groups. • Amantadine or rimantadine should not be administered as chemoprophylaxis against human infection with H5N1 if the virus is known or likely to be resistant. • Amantadine or rimantadine might be administered as chemoprophylaxis against human infection with H5N1 in high or moderate-risk exposure groups if neuraminidase inhibitors are not available and especially if the virus is known or likely to be susceptible. • Amantadine or rimantadine should probably not be administered as chemoprophylaxis against human infection with H5N1 virus in low-risk exposure groups if neuraminidase inhibitors are not available and even if the virus is known or likely to be susceptible.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer**[13] **(2010)**	Antiviral Prophylaxis • Yearly influenza vaccination with inactivated vaccine is recommended for all patients being treated for cancer. • Influenza virus infection should be treated with neuraminidase inhibitors if the infecting strain is susceptible. In the setting of an influenza exposure or outbreak, neutropenic patients presenting with influenza-like illness should receive treatment empirically.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the neuraminidase inhibitors are noted in Table 3. 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 3. FDA-Approved Indications for the Neuraminidase Inhibitors[1-5]

Indication	Oseltamivir	Zanamivir
Prophylaxis of influenza	✔ §	✔ *‡
Treatment of uncomplicated acute illness due to influenza infection	✔ §	✔ *†

§Efficacy in patients who begin treatment after 48 hours of symptoms has not been established.
†Not proven effective for treatment of influenza in individuals with underlying airways disease.
‡Not proven effective for prophylaxis of influenza in the nursing home setting.
*Not recommended for the treatment or prophylaxis of influenza in individuals with underlying airways disease.

IV. Pharmacokinetics

The pharmacokinetic parameters of the neuraminidase inhibitors are listed in Table 4.

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

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Oseltamivir	>75	3-42	Liver	Renal (>99) Feces (<20)	6-10
Zanamivir	4-25	Not reported	Minimal to none	Renal (4-17)	1.6-5.1

V. Drug Interactions

Significant drug interactions with the neuraminidase inhibitors are listed in Table 5.

Table 5. Significant Drug Interactions with the Neuraminidase Inhibitors[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Neuraminidase inhibitors	2	Influenza virus vaccine	Neuraminidase inhibitors may inhibit the replication of live vaccine virus thereby decreasing the production of influenza strain-specific antibodies.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the neuraminidase inhibitors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Neuraminidase Inhibitors[1-5]

Adverse Events	Oseltamivir	Zanamivir
Cardiovascular		
Angina	<1	-
Arrhythmia	✔	✔
Syncope	-	✔
Central Nervous System		
Abnormal behavior	✔	✔
Agitation	✔	✔
Anxiety	✔	✔
Confusion	✔	-
Consciousness altered	✔	✔
Delirium	✔	✔
Delusions	✔	✔
Dizziness	1-2	1-2
Fatigue	1-8	1-8
Fever/chills	<1	1-9
Hallucination	✔	✔
Headache	2-18	2-24
Hypothermia	✔	-
Insomnia	1	-
Malaise	-	1-8
Neuropsychiatric events	<1	-
Nightmares	✔	✔
Seizure	✔	✔
Vertigo	≤1	-
Dermatological		
Dermatitis	✔	-
Eczema	✔	-
Erythema multiforme	✔	✔
Rash	✔	✔
Stevens-Johnson syndrome	✔	✔
Toxic epidermal necrolysis	✔	✔
Urticaria	✔	<2
Gastrointestinal		
Abdominal pain	2-5	<2

Adverse Events	Oseltamivir	Zanamivir
Anorexia/appetite decreased	-	2-4
Appetite increased	-	2-4
Gastrointestinal bleeding	✔	-
Diarrhea	1-3	2-3
Hemorrhagic colitis	✔	-
Nausea	4-10	≤3
Pseudomembranous colitis	<1	-
Throat/tonsil discomfort/pain	-	8-19
Vomiting	2-15	1-2
Hepatic		
Hepatitis	✔	-
Liver function test abnormalities	✔	-
Musculoskeletal		
Arthralgia/articular rheumatism	-	≤2
Muscle pain	-	3-8
Myalgia	-	<2
Respiratory		
Asthma	-	<1
Bronchitis	1-2	2
Bronchospasm	-	✔
Cough	1-5	≤2-17
Dyspnea	-	✔
Ear, nose, and throat infections	-	<5
Epistaxis	1	-
Infection (ear/nose/throat)	-	1-5
Nasal inflammation	-	1
Nasal signs and symptoms	-	2-20
Sinusitis	-	3
Other		
Allergy	<1	-
Allergic or allergic-like reaction	-	✔
Anaphylactic/anaphylactoid reactions	✔	-
Conjunctivitis	1	-
Diabetes aggravation	✔	-
Facial edema	-	✔
Fracture	<1	-
Hemorrhage (ear/nose/throat)	-	<1
Oropharyngeal edema	-	✔
Swelling of face or tongue	✔	-
Viral infection	-	3-13

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the neuraminidase inhibitors are listed in Table 7.

Table 7. Usual Dosing Regimens for the Neuraminidase Inhibitors[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Oseltamivir	Prophylaxis of Influenza: Close contact and community outbreaks: 75 mg once daily for ≥10 days Treatment of Influenza: 75 mg twice daily for 5 days	Prophylaxis of Influenza: Close contact: ≥1 year of age: ≤15 kg: 30 mg once daily for at least 10 days 16-23 kg: 45 mg once daily for at least 10 days 24-40 kg: 60 mg once daily for at least 10 days ≥41 kg: 75 mg once daily for at least 10 days Treatment of Influenza: ≥1 year of age: ≤15 kg: 30 mg twice daily for 5 days 16-23 kg: 45 mg twice daily for 5 days 24-40 kg: 60 mg twice daily for 5 days ≥41 kg: 75 mg twice daily for 5 days	Capsule: 30 mg 45 mg 75 mg Suspension: 6 mg/ml 12 mg/ml
Zanamivir	Prophylaxis of Influenza: Household setting: 10 mg once daily for 10 days Community outbreaks: 10 mg once daily for 28 days Treatment of Influenza: 10 mg twice daily for 5 days	Prophylaxis of Influenza: ≥5 years of age: Household setting:10 mg once daily for 10 days Treatment of Influenza: ≥7 years of age: 10 mg twice daily for 5 days	Inhalation powder: 5 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the neuraminidase inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Neuraminidase Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Prophylaxis of Influenza				
Chik et al.[17] (2004) Oseltamivir 75 mg daily for 8 weeks (for prophylaxis)	OL, OS, PRO Patients with a mean age of 14, immuno-compromised through chemo-therapy or bone marrow trans-plantation	N=32 12 weeks	Primary: Diagnosis of influenza	Primary: Throughout the study period there were no laboratory confirmed cases of influenza infection.
Peters et al.[18] (2001) Oseltamivir 75 mg daily for 6 weeks beginning when influenza was detected locally vs placebo	DB, MC, PC, RCT Frail older occupants (mean age 81 years, >80% vaccinated) in residential homes across the United States and Europe	N=548 1998-1999 influenza season	Primary: Laboratory-confirmed clinical influenza Secondary: Adverse effects	Primary: Oseltamivir administration resulted in a 92% reduction in the incidence of laboratory-confirmed clinical influenza compared with placebo (4.4%), oseltamivir (0.4%; P=0.002). Of subjects vaccinated against influenza, oseltamivir was 91% effective in preventing laboratory-confirmed clinical influenza compared to placebo (5.0%), oseltamivir (0.5%; P=0.003). Oseltamivir use was associated with a significant reduction in the incidence of secondary complications compared to placebo (2.6%), oseltamivir (0.4%; P=0.037). Secondary: A similar incidence of adverse events, including gastrointestinal effects, occurred in both groups.
Welliver et al.[19] (2001) Oseltamivir 75 mg	DB, PC, RCT Households with an index contact (IC)	N=962 (377 households)	Primary: Proportion of contacts of an influenza-positive	Primary: For household contacts of infected ICs, the incidence of laboratory-confirmed clinical influenza for those receiving oseltamivir during the 7-day prophylaxis period was 0.8%, vs 12.9% in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for 7 days vs placebo	of any age, and with 2 to 8 other contacts >12 years of age; within <48 hours of symptom onset in the IC	7 days	IC with laboratory-confirmed clinical influenza during the dosing period; proportion of influenza cases in the test population as a whole Secondary: Number of households with additional influenza-related illnesses	This was calculated as a protective efficacy rate of 89% (95% CI: 67 to 97; P<0.001). For households with infected ICs, the proportions of households with at least 1 subsequently infected contact were 3.6% for the oseltamivir group vs 22.8% in the placebo group. This was calculated as a protective efficacy rate of 84% (95% CI: 49 to 95; P<0.001). Data was also collected in cases where the IC was not influenza as confirmed by laboratory tests, and in this group 0.4% of individuals taking oseltamivir came down with influenza from exposure in the community. A total of 3.1% of the placebo group developed influenza from community exposure. Protective efficacy for these individuals exposed to influenza outside the household was calculated at 89% (95% CI: 10 to 99; P=0.009). Twenty-one of the clinical cases among the placebo recipients were infected with influenza A and 13 with influenza B virus. None of the clinical cases in the group of oseltamivir-treated contacts was infected with influenza A virus, so protective efficacy was not calculated. The protective efficacy against influenza B illness in contacts of all ICs was calculated at 78.5% (P=0.02). Secondary: Frequency of individuals shedding virus and therefore more likely to transmit to others was significantly reduced in oseltamivir recipients compared with placebo. The protective efficacy in contacts of an influenza positive IC was calculated at 84% (95% CI: 57 to 95; P<0.001).
Hayden et al.[20] (1999) Oseltamivir 75 mg daily for six weeks	DB, MC, PC, RCT Healthy, non-immunized adults 18 to 65 years old from Virginia	N=1,559 1997-1998 influenza season	Primary: Laboratory-confirmed influenza-like illness	Primary: The risk of influenza among subjects assigned to either once-daily or twice-daily oseltamivir (1.2% and 1.3%, respectively) was lower than that among subjects assigned to placebo (4.8%; P<0.001 and P=0.001 for the comparison with once-daily and twice-daily oseltamivir, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or oseltamivir 75 mg twice daily for six weeks vs placebo	(Charlottesville, Norfolk, and Fairfax), Texas (Houston and Galveston) and Kansas (Kansas City) during the winter of 1997–1998		Secondary: Adverse effects	The protective efficacy of oseltamivir in the two active-treatment groups combined was 74% (95% CI: 53 to 88) at all the sites and 82% (95% CI: 60 to 93) at sites in Virginia, where the rate of influenza infection was higher than the overall rate. For culture-proven influenza, the rate of protective efficacy in the two oseltamivir groups combined was 87% (95% CI: 65 to 96). The rate of laboratory-confirmed influenza infection was lower with oseltamivir than with placebo (5.3% vs 10.6%, P<0.001). Secondary: Oseltamivir was well tolerated but was associated with a greater frequency of nausea (12.1% and 14.6% in the once-daily and twice-daily groups, respectively) and vomiting (2.5% and 2.7%, respectively) than was placebo (nausea, 7.1%; vomiting, 0.8%). However, the frequency of premature discontinuation of drug or placebo was similar among the three groups (3.1% to 4.0%).
Hayden et al.[21] (2004) Oseltamivir 75 mg twice daily for 10 days (postexposure prophylaxis[PEP]) vs oseltamivir 75 mg twice daily for 5 days at the time of developing illness (expectant treatment)	PG, PRO, RCT Household contacts of index cases presenting with an influenza-like illness ≥1 year of age	N=812 2000-2001 influenza season	Primary: Secondary spread of influenza	Primary: PEP provided a protective efficacy of 58.5% (95% CI: 15.6 to 79.6; P=0.0114) for households against proven influenza and 68.0% (95% CI: 34.9 to 84.2; P=0.0017) for individual contacts, compared with treatment of index cases alone. No oseltamivir-resistant variants were detected in treated index cases or contacts.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Jackson et al.[7] (2011) Oseltamivir vs zanamivir vs amantadine	MA Patients who received antiviral agents for the prevention of influenza	20 trials Variable duration	Primary: Prevention of symptomatic laboratory-confirmed influenza (SLCI) Secondary: Complications prevented, hospitalizations prevented, length of influenza illness and time to return to normal activities	Primary: Oseltamivir was efficacious in seasonal prophylaxis against (RR 0.24; 95% CI, 0.09-0.54). A protective effect of oseltamivir in seasonal prophylaxis was found in one study which included the frail elderly living in residential care (RR 0.08; 95% CI, 0.01-0.63). Oseltamivir was effective in preventing the transmission of SLCI in households of mixed composition (RR 0.19; 95% CI 0.08-0.45). Oseltamivir have a preventative effect against SLCI when employed as post-exposure prophylaxis in pediatric contacts (≥1 year of age; (RR 0.36; 95% CI, 0.15-0.84). Zanamivir demonstrated a protective efficacy of 68% for seasonal prophylaxis in adults (RR 0.32; 95% CI 0.17-0.63) and at-risk adolescents/adults (RR 0.17; 95% CI, 0.07-0.44). There was no significant different in older people with zanamivir. Zanamivir was effective in preventing the transmission of SLCI in households of mixed composition (RR 0.21; 95% CI, 0.13-0.33). There was no significant difference in the elderly in long-term care (RR 0.68; 95% CI 0.33-1.27). Evidence for the use of amantadine against SLCI in seasonal prophylaxis was limited. One trial demonstrated a non-significant preventative effect among healthy adults in seasonal prophylaxis (RR 0.40; 95% CI 0.08-2.03). Amantadine was effective in preventing SLCI in healthy adolescents (RR 0.10; 95% CI 0.03-0.34). Secondary: Oseltamivir seasonal prophylaxis was associated with a non-significant 78% reduction in secondary complications among at-risk elderly patients with laboratory-confirmed influenza (P=1.14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In a study of post-exposure prophylaxis, the proportion of contacts with laboratory-confirmed influenza with at least one secondary complication was equivalent among patients who received oseltamivir and those in the control arm who received expectant treatment upon the onset of influenza-like illness (7% versus 5%). However, the more severe respiratory complications occurred among the expectant treatment group. The median duration of illness in contacts was shorter in the oseltamivir post-exposure prophylaxis group versus those receiving treatment on influenza onset (5.5 hours versus 39.8 hours; P=0.103). Fewer contacts with laboratory-confirmed influenza in the oseltamivir post-exposure prophylaxis group were bedbound compared with patients in those receiving treatment on influenza onset (7% versus 28%). Significantly less work absence was reported among patients who received zanamivir as seasonal prophylaxis versus control group patients (mean hours lost 0.6 vs 1.4; P=0.001). Total productive time lost was also less in the zanamivir group (1.8 vs 3.0 hours; P=0.001). Significantly fewer households who received zanamivir post-exposure prophylaxis reported a contact developing a complication of laboratory-confirmed influenza (2% vs 6%;P=0.01). Complications of SLCI during the first 28 days following postexposure prophylaxis initiation were lower among the zanamivir-treated patients versus placebo (5% vs 6%; P=0.653). The proportion of cases with complications requiring antibiotics was marginally lower among patients receiving zanamivir post-exposure prophylaxis compared with placebo (5% vs 8%). Among household contacts with laboratory-confirmed influenza, the median time to alleviation of symptoms without use of medication was 5.5 days in the prophylaxis and 8.0 days in the placebo groups. Mean duration of significant influenza-like symptoms was shorter in the zanamivir post-exposure prophylaxis versus placebo group (0.2 vs 0.6 days; P=0.016).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No secondary outcomes were described relating to the use of amantadine in seasonal prophylaxis. Limited evidence was identified for milder influenza illness of shorter duration as a result of the use of amantadine in post-exposure prophylaxis. The severity of symptoms was reported as 56.0% mild and 9.0% severe in the amantadine group, and 38.0% mild and 19.0% severe in the placebo group (P<0.01 for severe symptoms, P<0.001 for mild symptoms). Mean duration of illness was found to be shorter in the amantadine group versus the placebo group (P<0.05).
Hayden et al.[22] (2000) Zanamivir 10 mg inhaled daily for 10 days in household contacts as prophylaxis vs placebo If an influenza-like illness developed in one member, the family was randomly assigned to receive either inhaled zanamivir or placebo. Infected family	DB, PC Families with two to five members and at least one child who was 5 years of age or older	N=1,158 1998-1999 influenza season	Primary: The proportion of families with at least one household contact with symptomatic, laboratory-confirmed influenza Secondary: Zanamivir-resistant variants and the median duration of symptoms in the index cases	Primary: The proportion of families with at least one initially healthy household contact in whom influenza developed was smaller in the zanamivir group than in the placebo group (4% vs 19%, P<0.001); the difference represented a 79% reduction in the proportion of families with at least one affected contact. Secondary: Zanamivir provided protection against both influenza A and influenza B. A neuraminidase-inhibition assay and sequencing of the neuraminidase and hemagglutinin genes revealed no zanamivir-resistant variants. Among the subjects with index cases of laboratory-confirmed influenza, the median duration of symptoms was 2.5 days shorter in the zanamivir group than in the placebo group (5.0 vs 7.5 days, P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
members (index) were treated with either 10 mg of inhaled zanamivir or placebo.				
Monto et al.[23] (2002) Zanamivir 10 mg inhaled daily for 10 days in household contacts as prophylaxis vs placebo Index patients received relief medication only.	DB, MC, PC, RCT Once a person with a suspected case of influenza was identified (index patient), treatment of all other household members (contacts) ≥5 years old was initiated; eligible households were composed of 2-5 members, with at least 1 adult >18 years old and 1 child 5-17 years old	N=1,778 11 months	Primary: Household contacts that developed symptomatic, laboratory-confirmed influenza	Primary: Four percent of zanamivir-treated patients vs 19% of placebo households had at least 1 contact who developed symptomatic, laboratory-confirmed influenza, representing 81% protective efficacy (95% confidence interval, 64% to 90%; P<0.001). Protective efficacy was similarly high for individuals (82%) and against both influenza types A and B (78% and 85%, respectively, for households). Zanamivir was well tolerated and was effective in preventing influenza types A and B within households where the index patient was not treated.
Monto et al.[24] (1999) Zanamivir 10 mg inhaled daily for 4 weeks vs placebo	DB, PC, RCT Healthy adults 18-69 years	N=1,107 1997-1998 influenza season	Primary: Laboratory-confirmed clinical influenza occurrence Secondary: Adverse effects	Primary: Zanamivir was 67% efficacious (95% CI: 39 to 83; P<0.001) in preventing laboratory-confirmed clinical influenza meeting the case definition and 84% efficacious (95% CI: 55 to 94; P=0.001) in preventing laboratory-confirmed illnesses with fever. All influenza infections occurring during the season, with or without symptoms, were prevented with an efficacy of 31% (95% CI: 4 to 50; P=0.03). Secondary: The nature and incidence of adverse events in the zanamivir group did not differ from placebo. Adverse effects thought by the investigators to be potentially drug-related were observed in 27 (5%) of the placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group and 30 (5%) of the zanamivir group. Potential adverse effects that were considered severe were seen in 1 (<1%) of the placebo recipients and 1 (<1%) of the zanamivir recipients.
Halloran et al.[25] (2007) Neuraminidase inhibitors (NI) for postexposure prophylaxis vs placebo	MA Individuals >1 year of age who were household contacts of an individual diagnosed with influenza	N=3,902 4 RCT 14 days or more	Primary: Efficacy in preventing illness, reduction in infectiousness, reduction in pathogenicity	Primary: Efficacy against illness was demonstrated with zanamivir (75%, 95% CI: 54 to 86) and oseltamivir (81%, 95% CI: 35 to 94). In zanamivir-treated patients, the effect on reducing infectiousness was 19% (95% CI: -160 to 75) compared to 80% (95% CI: 43 to 93) for oseltamivir. In reducing the pathogenicity, the efficacy of zanamivir was 52% (95% CI: 19 to 72) and 56% (95% CI: 14 to 77) in two studies, compared to 56% (95% CI: 10 to 73) and 79% (95% CI: 45 to 92) for two other studies with oseltamivir.
LaForce et al.[16] (2007) Zanamivir 10 mg inhaled once daily for 28 days vs placebo	RCT, DB, MC, PC Community-dwelling patients aged ≥12 years who were at high risk (defined as age ≥65 years or the presence of chronic disorders of the pulmonary or cardiovascular system or diabetes mellitus) for developing complications of influenza	N=3363 36-49 days	Primary: Proportion of patients who developed symptomatic influenza A or B infection during prophylaxis as confirmed by culture and/or serology Secondary: Patients with culture/serology-confirmed influenza who developed symptomatic	Primary: Four (0.2%) of 1678 zanamivir-treated subjects developed symptomatic culture/serology-confirmed influenza between day 1 and day 28, compared with 23(1.4%) of 1685 placebo recipients (RR 0.17; 95% CI, 0.07-0.44; P<0.001). Secondary: A significant difference in the incidence of symptomatic, laboratory-confirmed influenza in favor of zanamivir was seen in the per-protocol population (P=0.014), as well as in subjects who developed symptomatic, laboratory-confirmed influenza between days 2 and 28 (P<0.001) and days 3 and 28(P=0.001). These results represented protective efficacies of 75%, 81%, and 80%, respectively. Significantly fewer zanamivir-treated subjects than placebo recipients developed laboratory-confirmed influenza with recorded fever (6/1678 vs 16/1685, respectively; P=0.050; RR=0.37; 95% CI, 0.15-0.92).This result represented a protective efficacy of 63%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			influenza A or B during prophylaxis, with symptoms beginning on day 2/3 or later, fever, complication of influenza, patients who developed ILI, and patients who had laboratory-confirmed influenza regardless of symptoms	Confirmed influenza with complications occurred in1 of 1678 subjects in the zanamivir group and 8 of 1685 subjects in the placebo group (RR 0.12; 95% CI, 0.02-0.73; P=0.042). This result represented a protective efficacy of 88%. The numbers of zanamivir recipients (9%) and placebo recipients (10%) who developed symptomatic ILI regardless of laboratory confirmation did not differ significantly (RR 0.86;95% CI, 0.70-1.06). There was no significant difference in the numbers of zanamivir and placebo recipients who developed laboratory-confirmed infection regardless of symptoms (2% and 3%, respectively; RR 0.76; 95% CI, 0.50-1.15).
Treatment of Influenza				
Aoki et al.[26] (2003) Oseltamivir 75 mg twice a day for 5 days	MC, OL Patients (12-70 years of age) presenting within 48 hours of the onset of influenza symptoms	N=1,426 1999-2000 influenza season	Primary: Illness duration Secondary: Duration of fever, severity of symptoms, time to return to baseline activity	Primary: Earlier intervention was associated with shorter illness duration (P<0.0001). Initiation of therapy within the first 12 hours after fever onset reduced the total median illness duration by 74.6 hours (3.1 days; 41%) more than intervention at 48 hours. Secondary: The early administration of oseltamivir further reduced the duration of fever (P=0.0115), severity of symptoms (P=0.0023) and the times to return to baseline activity (P=0.001).
Machado et al.[27] (2004) Oseltamivir 75 mg twice a day for 5 days	OL, PRO Patients with a proven upper or lower respiratory tract influenza infection detected by direct immuno-	N=66 1 year	Primary: Complications of influenza	Primary: The percent of patients who developed influenza-related pneumonia after the initiation of oseltamivir within 48 hours of symptoms appearing was 5.1% and no patients died of influenza.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	fluorescence assay			
Singh et al.[28] (2003) Oseltamivir 75 mg twice a day vs placebo	MA Individuals aged 13-97 presenting within 36 hours of onset of influenza symptoms	N=2,413 Specific duration varied	Primary: Alleviation of illness, return to normal health status, ability to perform usual activities, normal sleep patterns, symptom improvement, duration of illness	Primary: When compared to placebo, the time to alleviation of illness was reduced by 19% (median duration 100.6 hours [95% CI: 94.8 to 104.7] vs 124.5 hours [95% CI: 117.7 to 132.3]; P<0.00010). When compared to placebo, individuals who received oseltamivir returned to normal health status, regained ability to perform usual activities and regained normal sleep patterns significantly faster. When compared to placebo, treatment with oseltamivir significantly reduced fatigue by 29% and myalgia by 26% (P<0.0001). More placebo- than oseltamivir-treated patients (57%) remained febrile after 48 hours of treatment. The median duration of acute febrile illness was significantly shortened by use of oseltamivir when compared to placebo in patients with cardiac disease (44 hours vs 64.7 hours, P=0.026) and chronic obstructive pulmonary disease (37.9 hours vs 53.8 hours, P=0.004).
Kawai et al.[29] (2006) Oseltamivir 75 mg twice a day for 5 days vs placebo	MC, PRO Patients who reported influenza-like illness	N=3303 5 days	Primary: Duration of fever	Primary: Patients with influenza A and influenza B who were treated with oseltamivir had a significantly shorter duration of fever compared to patients who were not treated with oseltamivir (P<0.001). The duration of fever was significantly longer among oseltamivir-treated patients who had influenza B compared to influenza A (65.4 hours vs 47.9 hours, P<0.001). For patients with influenza B compared to patients with influenza A, the duration of fever, measured from the time at which the first dose of oseltamivir was administered, was significantly longer at all time points (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				For patients with influenza B compared to patients with influenza A, the duration of fever from the time at which the first dose of oseltamivir was administered was significantly longer in all age groups (P<0.001).
Kaiser et al.[30] (2003) Oseltamivir 75 mg twice a day for 5 days vs placebo	MA Patients 13-97 years of age with influenza like illnesses	N=3,564 28 days	Primary: The occurrence of lower respiratory tract complications (LRTCs) requiring intervention Secondary: Hospitalizations, upper respiratory tract complications (URTCs), overall antibiotic use	Primary: Among influenza-infected patients, oseltamivir reduced the incidence of LRTCs leading to antibiotic intervention by 55% compared with placebo (4.6% vs 10.3%, P<0.001). Secondary: The overall percentage of patients hospitalized for any cause was 1.7% in the placebo group compared to 0.7% in the oseltamivir group (59% reduction, P=0.02). A reduction of 50% in overall hospitalizations was seen in the oseltamivir-treated, influenza-infected at-risk patients compared with placebo (1.6% vs 3.2%; P=0.17). The overall incidence of respiratory events following influenza infection was reduced by 28% in the oseltamivir group when compared to placebo (11.9% vs 16.9%, P=0.001). No difference was observed in physician diagnosed URTCs leading to antibiotic use between the two treatment groups.
Lin et al.[31] (2006) Oseltamivir 75 mg twice a day for 5 days vs symptomatic	OL, RCT Chinese patients at high risk initiating treatment within 48 hours after symptom onset	N=56 5 days of treatment, follow-up varied	Primary: Duration and severity of illness Secondary: Incidence of complications, antibiotic use, hospitalizations	Primary: The duration and severity of influenza symptoms was significantly reduced in the oseltamivir group, by 36.8% (P=0.0479) and 43.1% (P=0.0002) respectively. Secondary: The duration of fever was significantly reduced in the oseltamivir group by 45.2% (P=0.0051), as was the proportion that returned to baseline health status within 5 days (11% vs 45%, P=0.0011).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treatment				In the oseltamivir group, the incidence rates of complications (11% vs 45%, P=0.0053) and antibiotic use (37% vs 69%, P=0.0167) were significantly lower.
Lee et al.[53] (2010) Oseltamivir 75 mg twice daily for 5 days vs no antiviral treatment	PRO, OBS Hospitalized patients ≥18 years of age with laboratory-confirmed seasonal influenza infection.	N=754 Variable duration	Primary: Clinical outcomes	Primary: Supplemental oxygen and ventilatory support was required in 53.2% and 5.4% of patients, respectively. A total of 5.2% of patients died, which were due to pneumonia, respiratory failure and sepsis. A total of 52% of patients received oseltamivir treatment. Omission of antiviral treatment was associated with delayed presentation or negative antigen detection results. The mortality rate was 4.56 and 7.42 per 1000 patient-days in the treated and untreated patients, respectively. Antiviral use was associated with reduced risk of death (HR, 0.27; 95% CI, 0.13 to 0.55; P<0.001). Improved survival was observed with treatment started within 4 days from onset. Earlier hospital discharge (HR, 1.28; 95% CI, 1.04 to 1.57; P=0.019) and faster discontinuation of oxygen therapy (HR, 1.30; 95% CI, 1.01 to 1.69; P=0.043) was associated with early treatment within 2 days.
Ng et al.[54] (2010) Oseltamivir vs no therapy	OL Patients who reported ≥2 symptoms of acute respiratory illness (ARI) with symptom onset within 48 hours and	N=384 (index patients and household contacts) 7-10 days	Primary: Clinical outcomes	Primary: Index patients who had taken oseltamivir within 24 hours of symptom onset experienced a 44% reduction in time to alleviation of all signs and symptoms, with an adjusted acceleration factor of alleviation of 0.56 (95% CI, 0.42–0.76) compared with index patients who did not take any antiviral. Results were similar for time to alleviation of fever and time to alleviation of respiratory symptoms. The median duration of viral shedding after symptom onset was 6

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	lived with at least 2 other individuals, none of whom had reported ARI symptoms during the previous 14 days			days, and viral shedding resolved sooner in individuals prescribed oseltamivir within 24 hours of onset. Index patients who took oseltamivir within 48 hours of onset had a non-significant reduction in duration of viral shedding in year 2007 (acceleration factor, 0.76; 95% CI, 0.51–1.14) and 2008 (acceleration factor, 0.99; 95% CI, 0.83–1.17) compared with index patients who did not take any antiviral medication. Among the 331 households with a single index patient, influenza virus infection was confirmed by RT-PCR or viral culture in 80 of 989 household contacts, corresponding to an overall SAR of 8.1% (95% CI, 6.5%-10%). Stratifying by groups, the SAR was 4.7% (95% CI, 1.0%-13%), 6.0% (95% CI, 2.5%-12%), and 7.0% (95% CI, 1.5%-19%) in household contacts of index patients who had taken oseltamivir within 24 hours, 24–48 hours, and 148 hours after symptom onset, respectively, compared with 8.7% (95% CI, 6.8%-11%) in the no antiviral group (P<0.01). Household contacts of index patients who took oseltamivir within 24 hours of first symptoms had a non-significant lower risk of developing influenza virus infection confirmed by RT-PCR or viral culture (adjusted OR, 0.54; 95% CI, 0.11–2.57), clinical influenza (adjusted OR, 0.52; 95% CI, 0.25–1.08), and clinical influenza confirmed by RT-PCR or viral culture (adjusted OR, 0.47; 95% CI, 0.05– 4.03). The risk reduction was attenuated for the contacts of index patients who had taken oseltamivir later than 24 hours after symptom onset (P=0.09 for laboratory-confirmed influenza and P=0.41 for clinical influenza). Household contacts were at lower risk of illness from influenza virus infection if they had been vaccinated, if they were older, or if their corresponding index patient was older.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sugaya et al.[32] (2007) Oseltamivir twice a day for 5 days (weight-based dosing) vs control	OL Children aged 1-15 years presenting to outpatient clinics within 48 hours of onset of symptoms	N=489 5 days	Primary: Total febrile period, duration of fever, virus shedding	Primary: When comparing the study participants with influenza A to those with influenza B, there was a significant difference in the mean duration of febrile period (2.19 days vs 4.44 days, P<0.001). In patients with influenza B, the mean duration of febrile period significantly differed between the patients treated with oseltamivir and the control patients (2.98 days vs 5.55 days, P<0.001). The mean duration of fever after the initiation of therapy was 1.31 days with influenza A patients compared to 2.18 days with influenza B patients (P<0.001). For patients with influenza B, the duration of fever was significantly longer in children 1-5 years of age (2.37 days) than in children 6-10 years of age (1.97 days, P=0.013) and 11-15 years of age (1.54 days, P=0.006). The difference between children 6-10 and 11-15 years of age was not significant (P=0.14). There was a significant difference in the duration of fever in the two younger groups of children between the patients with influenza A and B (children 1-5, 1.42 days vs 2.37 days, P<0.001 and children 6-10, 1.23 days vs 1.97 days, P<0.001). There was no significant difference in duration of fever with influenza A vs influenza B in the group of children aged 11-15 (P=0.54). There was no significant difference either for the total population or for the subgroups by age in the duration of fever between patients with influenza A who had been vaccinated and those who had not (1.36 days vs 1.36 days). There was a significant difference in mean virus titers two days after the start of oseltamivir between the influenza A and influenza B groups (0.61 vs 2.84, P<0.001).
Whitley et al.[33]	DB, PC, RCT	N=695	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Oseltamivir liquid 2 mg/kg/dose twice daily for 5 days vs placebo	Children 1 through 12 years with fever and a history of cough or coryza <48 hours duration	1998-1999 influenza season	Time to resolution of illness including mild/absent cough and coryza mild/absent, return to normal activity and euthermia Secondary: Adverse effects	Among infected children, the median duration of illness was reduced by 36 hours (26%) in oseltamivir recipients compared with placebo recipients (101 hours; 95% CI: 89 to 118 vs 137 hours; 95% CI: 125 to 150; P<0.0001). Oseltamivir treatment also reduced cough, coryza and duration of fever. New diagnoses of otitis media were reduced by 44% (12% vs 21%). The incidence of physician-prescribed antibiotics was significantly lower in influenza-infected oseltamivir (68 of 217, 31%) than placebo (97 of 235, 41%; P=0.03) recipients. Secondary: Oseltamivir therapy was generally well-tolerated, although associated with an excess frequency of emesis (5.8%). Discontinuation because of adverse events was low in both groups (1.8% with oseltamivir vs 1.1% with placebo).
Nicholson et al.[34] (2000) Oseltamivir 75 mg twice daily for 5 days vs oseltamivir 150 mg twice daily for 5 days vs placebo	RCT Adults with naturally acquired laboratory-confirmed influenza with febrile influenza-like illness of up to 36 hours duration	N=726 3 months	Primary: Time to resolution of illness Secondary: Symptom scores, viral shedding, health, activity, sleep quality, and tolerability	Primary: Duration of illness was significantly shorter by 29 hours (25% reduction, median duration 87.4 hours [95% CI: 73.3 to 104.7], P=0.02) with oseltamivir 75 mg and by 35 hours (30%, 81.8 hours [95% CI: 68.2 to 100.0], P=0.01) with oseltamivir 150 mg, both in comparison to placebo (116.5 hours [95% CI: 101.5 to 137.8]). The effect of oseltamivir was apparent within 24 hours of the start of treatment. In patients treated within 24 hours of symptom onset, symptoms were alleviated 43 hours (37% reduction) and 47 hours (40%) earlier with oseltamivir 75 mg and 150 mg, respectively, compared with placebo (for 75 mg, time to symptom alleviation=74.5 hours [95% CI: 68.2 to 98.0], P=0.02; for 150 mg, time to symptom alleviation=70.7 hours [95% CI: 54.0 to 89.4], P=0.01; for placebo, time to symptom alleviation=117.5 hours [95% CI: 103.0 to 143.8]). Secondary: Oseltamivir was associated with lower symptom scores, less viral shedding, and improved health, activity, and sleep quality, and was well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treanor et al.[35] (2000) Oseltamivir 75 mg twice daily for 5 days vs oseltamivir 150 mg twice daily for 5 days vs placebo for 5 days	DB, MC, RCT Adults aged 18 to 65 years presenting within 36 hours of onset of influenza symptoms	N=629 21 days	Primary: Duration of illness, defined as the time to the beginning of the first 24-hour period in which all influenza symptoms were rated as mild or less Secondary: Duration and severity of individual symptoms, incidence of secondary complications, quantity of viral shedding	Primary: The median durations of illness were 103.3 hours (4.3 days) in the placebo group, and 71.5 hours (3.0 days) and 69.9 hours (2.9 days) in the 75 mg and 150 mg oseltamivir groups, respectively. Treatment with oseltamivir at either 75 or 150 mg twice daily resulted in statistically significant reductions (P<0.001 and P=0.006, respectively) in the area under the curve (AUC) analysis of total symptom scores which reflects the severity and duration of illness. There were no differences between the 2 doses of oseltamivir with regard to effects. The 75 mg and 150 mg doses of oseltamivir reduced the severity of illness compared to placebo by 38% and 35%, respectively (P<0.001 for both). Secondary: Duration of cough was reduced from a median of 55 hours in the placebo group to 31 hours (43% reduction) in the 75 mg group and to 40 hours (27% reduction) in the 150 mg group. The duration of myalgia was also reduced, from a median of 28 hours in placebo recipients to 16 hours (42% reduction) in the 75 mg group and 19 hours (32% reduction) in the 150 mg group. After 24 hours of treatment, median viral titers had decreased by 1.2 logs in the placebo group vs 1.7 and 2.0 logs in the 75 mg and 150 mg oseltamivir groups, respectively. These differences were not statistically significant. Nausea and vomiting occurred more frequently in both the oseltamivir groups compared to placebo (P<0.001).
Kawai et al.[50] (2009)	OL Patients with H1N1	N=373 5 days	Primary: Efficacy and safety	Primary: The duration of fever after the start of oseltamivir therapy was significantly longer for patients with H1N1 virus infection during the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Oseltamivir 75 mg for adults and 2 mg/kg for children <37.5 kg twice daily for 5 days vs zanamivir 10 mg twice daily for 5 days	or H3N2 virus infection			2008–2009 season than it was for those with infection during the 2007–2008 season (P<0.001) and for patients with H3N2 virus during the 2008–2009 season (P<0.01). No significant difference was found in the duration of fever after the start of zanamivir therapy among the 3 groups with H1N1 virus infection during the 2007–2008 season, H1N1 virus infection during the 2008–2009 season, or H3N2 virus infection during the 2008–2009 season. The duration of fever after the start of oseltamivir therapy for patients in the ≤15-year-old and >15-year-old age groups was significantly longer for patients of both groups in 2008– 2009 than in patients with H1N1 virus in 2007–2008. The duration of oseltamivir therapy in the 2008–2009 season was significantly longer than that of zanamivir therapy in each age group in the 2008–2009 season (P<0.001 and P<0.01, respectively). The duration of fever after onset of symptoms was significantly longer for patients with H1N1 virus infection in the 2008–2009 season than for patients with H1N1 virus infection in the 2007–2008 season and for patients with H3N2 virus infection in the 2008– 2009 season. A significant difference was found between oseltamivir and zanamivir therapy for patients with H1N1 virus infection in the 2008–2009 season (P<0.001). The duration of fever for patients treated with oseltamivir was significantly longer during the 2008–2009 season than it was during the 2007–2008 season for patients ≤15 years old (P<0.01) but was not statistically significant for patients >15 years old. The duration of zanamivir therapy was significantly shorter than the duration of oseltamivir therapy in both age groups in the 2008–2009 season. The percentages of febrile patients at 48 and 72 hours after oseltamivir therapy were significantly higher in the H1N1 virus infection group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				during 2008–2009 than in the H1N1 virus infection group during 2007–2008 or the H3N2 virus group during the 2008–2009 season in all age groups. The percentage of febrile patients at 48 and 72 hours after oseltamivir therapy for the H1N1 virus infection group during the 2008–2009 season was also significantly higher than for the H1N1 virus group during 2007–2008 for children <10 years old.
Sugaya et al.[55] (2008) Oseltamivir (weight-based dosing) twice daily for 5 days vs zanamivir 20 mg/day given twice daily for 5 days	OL Children with influenza A (H1N1) virus, influenza A (H3N2) virus, and influenza B virus infections	N=162 5 days	Primary: Total febrile period and the duration of fever after the start of treatment	Primary: In patients with influenza A (H3N2), there was no significant difference in total febrile period or duration of fever after the start of treatment with oseltamivir and zanamivir (mean duration of febrile period, 2.40 days vs 2.39 days; mean duration of fever after the start of treatment, 1.35 days vs 1.40 days). The total febrile period was shortened by ~2 days with oseltamivir (P<0.05) and zanamivir (P<0.05). There were no significant differences in the body temperature among the groups. In patients with influenza A (H1N1), there was no significant difference in total febrile period or the duration of fever after the start of treatment between the treatment groups (mean duration of febrile period, 2.60 days vs 2.46 days; mean duration of fever after the start of treatment, 1.79 days vs 1.54 days). There were no significant differences in the body temperature among the groups. In patients with influenza B, there was no significant difference in total febrile period or duration of fever after the start of treatment between the treatment groups (mean duration of febrile period, 2.95 days vs 2.84 days; mean duration of fever after the start of treatment, 1.86 days vs 1.67 days). The total febrile period was shortened by ~1 day with oseltamivir (P<0.05) and with zanamivir (P<0.05). There were no significant differences in the body temperature among the groups.
Shun-Shin et al.[49] (2009) Oseltamivir	MA Children ≤12 years of age with	N=2,629 (7 trials) Variable	Primary: Time to resolution of illness and incidence of	Primary: Treatment with zanamivir and oseltamivir provided a median reduction in time to resolution of symptoms of between 0.5 and 1.5 days.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs zanamivir	influenza	duration	influenza in children living in households with index cases of influenza	A 10 day course of prophylaxis with either zanamivir or oseltamivir was associated with an 8% reduction in the risk of developing confirmed symptomatic influenza after the introduction of an index case of clinical influenza into the household (P<0.001). This equates to a number needed to treat of 13to prevent one additional household case of symptomatic influenza. Oseltamivir did not reduce asthma exacerbations or improve peak flow in children with asthma in on trial. Treatment was not associated with reduction in overall use of antibiotics. Zanamivir was well tolerated, but oseltamivir was associated with an increased risk of vomiting (number needed to harm=20).
Jefferson et al.[51] (2009) Oseltamivir vs zanamivir vs placebo, control antivirals, or no intervention	MA Healthy people exposed to naturally occurring influenza	20 trials Variable duration	Primary: Influenza or influenza-like illness	Primary: Evidence was insufficient to support or refute the effect of neuraminidase inhibitors on prophylaxis of influenza-like illness (RR 1.28; 95% CI, 0.45 to 3.66 for oseltamivir; RR, 1.51; 95% CI, 0.77 to 2.95 for zanamivir). Zanamivir reduced the chance of symptomatic laboratory confirmed influenza (RR, 0.38; 95% CI, 0.17 to 0.85 for 10 mg daily). Oseltamivir was similarly efficacious (RR, 0.39; 95% CI, 0.18 to 0.85 for 75 mg daily). Neither protected against asymptomatic influenza. Two zanamivir trials reported significant protection for households (RR, 0.1930 and RR, 0.219) and two oseltamivir trials reported similar results (RR, 0.1634 and RR, 0.4218). There was evidence of benefit in shortening the duration of influenza-like illness for zanamivir (HR, 1.24; 95% CI, 1.13 to 1.36) and for oseltamivir (HR, 1.20; 95% CI, 1.06 to 1.35) if taken within 48 hours of the onset of symptoms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Oseltamivir induced nausea (OR, 1.79; 95% CI, 1.10 to 2.93).
Kimberlin et al.[52] (2010) Oseltamivir vs amantadine vs rimantadine	RETRO Children <12 months of age with influenza	N=180 Variable duration	Primary: Frequency of neurologic adverse events and all adverse events	Primary: Abnormalities that potentially reflected neurologic involvement were consistent with influenza disease, related to preexisting underlying neurologic conditions, or explainable by a concomitant medication. Two patients had possible seizures or seizure-like movements during therapy with no preexisting history of such events, but in both cases the seizures were not thought to be related to antiviral therapy. Only 33% of the patients had Glasgow Coma Score (GCS) information available in their medical records. The end-of-treatment ranked verbal score was slightly lower for oseltamivir treated patients (P=0.04). Total scores were identical between the 2 therapies (P=0.40). One death occurred within 30 days following initiation of the influenza antiviral medications.
Nordstrom et al.[36] (2005) <u>Group 1</u> Oseltamivir with a diagnosed influenza-like illness (ILI) vs <u>Group 2</u> oseltamivir with no diagnosis of ILI vs	RETRO Patients receiving oseltamivir or with a diagnosis of ILI	N=89,192 December 1999 – March 2002	Primary: Diagnosis of pneumonia, hospitalization for any cause, dispensing of an antibiotic	Primary: When comparing ILI with oseltamivir to ILI with no antivirals, the adjusted hazard ratio for pneumonia was 0.72 (95% CI: 0.60 to 0.86), for antibiotic dispensing was 0.89 (95% CI: 0.86 to 0.93), and for hospitalization was 0.74 (95% CI: 0.61 to 0.90).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Group 3 no antiviral therapy and diagnosed with ILI				
Johny et al.[37] (2002) Zanamivir 10 mg twice a day until excretion of virus ceased	OL Patients post allograft with diagnosed influenza	N=7 5-44 days	Primary: Toxicity, morbidity	Primary: With the administration of zanamivir there were no toxicity attributes noted and there was no mortality seen in the 7 patients.
MIST Study Group[38] (1998) Zanamivir 10 mg inhaled twice daily for 5 days vs placebo	DB, MC, RCT Healthy individuals 12 years or older presenting with influenza-like illness of 36 hours duration or less	N=455 28 days	Primary: Length of time to alleviation of clinically important symptoms including absence of fever, mild headache, cough, myalgia and sore throat for 24 hours Secondary: Length of time to return to normal activities, mean symptom scores, sleep disturbance, use of relief medications, rate of complications and associated use	Primary: Zanamivir significantly shortened the time to alleviation of symptoms in the intention-to-treat population compared with placebo (5.0 vs 6.5 days P=0.011). This 1.5 day benefit was seen also for influenza-positive patients (4.5 vs 6.0 days, P=0.004). In patients who were febrile and received zanamivir, symptoms were decreased 2.0 days earlier than in those on placebo (P<0.001) in the intention-to-treat and influenza-positive patient groups. Influenza-positive patients treated with zanamivir had significantly less severe symptoms overall on days 1-14 than those on placebo (P<0.05). High-risk patients had significantly fewer complications than those on placebo (P=0.004) and fewer high risk patients needed antibiotic medication to treat those complications (P=0.025). Secondary: When zanamivir recipients were compared to patients on placebo, return to normal activities, sleep disturbances, complication rates, and associated use of antibiotics were all less in the intention-to-treat and influenza-positive populations, but the differences were not significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			of antibiotics	
Hedrick et al.[39] (2000) Zanamivir 10 mg inhaled twice daily for 5 days vs placebo	DB, MC, PC, RCT Children 5 to 12 years of age with influenza-like symptoms for ≤36 hours	N=471 1998-1999 influenza season	Primary: Alleviation of symptoms Secondary: Return to normal activities, use of relief medications, adverse events	Primary: A total of 346 (73%) patients were influenza-positive by culture, serology or polymerase chain reaction (65% influenza A, 35% influenza B). Zanamivir reduced the median time to symptom alleviation by 1.25 days compared with placebo among patients with confirmed influenza infection (P<0.001). Secondary: Zanamivir-treated patients returned to normal activities significantly faster than placebo (influenza-positive population, P=0.022; intent-to-treat population, *P*=0.019). The zanamivir-treated patients also took significantly fewer relief medications than those treated with placebo in the influenza-positive (P=0.005) and intent-to-treat (P=0.016) populations. Zanamivir was well-tolerated, demonstrating adverse event profiles similar to those of placebo and no clinically significant changes in laboratory findings. Adverse events were reported during treatment for 21% for patients in the zanamivir group and 26% of patients in the placebo group.
Lalezari et al.[40] (2001) Zanamivir 10 mg twice daily for 5 days vs placebo	MA High risk patients with confirmed influenza	N=321 21-28 days	Primary: Time to return to normal activities, median time to alleviation of symptoms	Primary: A treatment benefit of 2.5 days was seen with the zanamivir-treated high risk patients compared to placebo (P=0.015). Patients returned to normal activities 3 days earlier (P=0.022) and had an 11% reduction (P=0.0.9) in the median total symptom score over 1-5 days of treatment with zanamivir compared to placebo. The incidence of complications requiring antibiotic use was reduced by 43% with treatment with zanamivir compared to placebo (P=0.045). Adverse events were similar between the treatment groups.
Hayden et al.[41]	DB, RCT	N=417	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1997) Zanamivir 6.4 mg by intranasal spray* plus 10 mg by inhalation twice a day for 5 days vs zanamivir 10 mg by inhalation plus placebo spray twice a day for 5 days vs placebo by both routes twice a day for 5 days	Adults with acute influenza of ≤48 hours duration	1994-1995 influenza season	Length of time to alleviation of all major symptoms	Of 262 patients with confirmed influenza-virus infection (63% of all patients), the median length of time to the alleviation of all major symptoms was one day shorter (four days vs five days) in the 88 patients given inhaled and intranasal zanamivir (P=0.02) and the 85 patients given inhaled zanamivir alone (P=0.05) than in the 89 patients given placebo. Among the infected patients who were febrile at enrollment and among those who began treatment within 30 hours after the onset of symptoms, the median time to the alleviation of major symptoms was four days in both zanamivir groups and seven days in the placebo group (P<0.01).
Monto et al.[42] (1999) Zanamivir 10 mg inhaled twice a day for 5 days vs zanamivir 10 mg inhaled 4 times a day for 5 days	DB, MC, PG, RCT Healthy persons aged ≥13 years who presented with symptoms of influenza ≤48 hours of duration	N=1,256 1995-1996 influenza season	Primary: Alleviation of all major symptoms Secondary: Nights of disturbed sleep, time to resumption of normal activities, use of symptom relief medications	Primary: In the overall population with or without influenza infection, zanamivir reduced the median number of days to alleviate all major symptoms by 1 day (P=0.012 two times daily vs placebo; *P*=0.014 four times daily vs placebo). The reduction was greater in patients treated within 30 hours of symptom onset, febrile at study entry, and in defined high-risk groups. Secondary: Zanamivir reduced nights of disturbed sleep (P=0.013; zanamivir 4 times a day vs placebo, P=0.026), time to resumption of normal activities (P=0.005; zanamivir 4 times a day vs placebo, P<0.001), and use of symptom relief medications (P<0.001; zanamivir 4 times a day

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				vs placebo, P=0.007).
Kawai et al.[43] (2005) Oseltamivir 75 mg for adults and 2 mg/kg for children <37.5 kg given twice a day for 5 days to patients with either influenza A (Group 1) or influenza B (Group 2) vs amantadine 50 mg for adults and 1.5-2.5 mg/kg for children administered twice daily for 5 days to patients with influenza A (Group 3)	OL Patients diagnosed with influenza who received oseltamivir or amantadine therapy within 48 hours after symptom onset	N=2,163 5 days	Primary: Time from onset of symptoms to start of treatment, duration of fever, impact of age on outcome	Primary: For all 3 groups, the duration of fever was significantly shorter in patients who received the medication within 12 hours after the onset of symptoms compared to greater than 12 hours after the onset of symptoms (P<0.001). For patients in Group 2, the duration of fever was significantly longer when compared to Groups 1 and 3; however, there was no significant difference between groups 1 and 3 (P<0.01 to <0.05). The duration of fever was significantly longer for patients in Groups 2 and 3 aged 0-6 years when compared to those aged 7-15 years and 16-64 years (P<0.001 to 0.01). The duration of fever of patients 0-6 years in Group 1 was significantly shorter than for those same aged patients in Group 2 (P<0.01). For patients aged 16-64 years and >65 years, there was no significant difference between groups in duration of fever (P=NS).
Kawai et al.[15] (2008) Zanamivir 10 mg (adults and	OL Patients with influenza-like illness (body	N=1,113 5 days 2006-2007	Primary: Duration of fever and percentage of patients afebrile at 24 and 48 hours	Primary: The duration of fever from its onset was significantly shorter for patients with influenza A who were treated with either zanamivir or oseltamivir than in those who were not treated with an anti-influenza drug (49.7 ± 21.7 or 52.5 ± 25.6 and 75.4 ± 24.2 h, respectively; both

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
children aged ≥5 years) twice daily for five days vs oseltamivir (75 mg for adults and children >37.5 kg;2 mg/kg for children <37.5 kg) orally twice daily for five days vs no treatment Antipyretics were not administered, and in the case of emergency, acetaminophen was used temporally.	temperature ≥37.5°C, upper respiratory tract symptoms, and systemic symptoms) who received a diagnosis of influenza A or B	influenza season	after the first dose	P<0.001). For patients with influenza B, the duration of fever from its onset was significantly shorter for patients who were treated with zanamivir than for those who were treated with oseltamivir or not treated with an anti-influenza drug (53.9 ± 26.4 and 69.4 ± 32.9 or 75.3 ± 27.3 h, respectively; both P<0.001). Among oseltamivir recipients, the duration of fever was significantly longer for patients with influenza B than for patients with influenza A (69.4 ± 32.9 and 52.5 ± 25.6 h, respectively; P<0.001). For patients with influenza A aged 5-10 years, no significant difference in the duration of fever was shown between zanamivir and oseltamivir therapy (35.4 ± 23.2 and 30.8 ± 20.2 h, respectively). For all patients with influenza A and patients with influenza A aged >10 years, the duration of fever was significantly shorter with zanamivir therapy than with oseltamivir therapy (31.8 ± 18.4 and 35.5 ± 23.9 h; P<0.05 in all patients, and 31.0 ± 17.0 and 37.1 ± 24.9; P<0.001 in patients aged >10 years, respectively). For patients with influenza B, the duration of fever was significantly shorter for patients treated with zanamivir than with oseltamivir in all patients, in patients aged 5-10 years, and in patients aged >10 years (all P<0.001). For patients with influenza A, no significant differences in the percentage of patients afebrile at 24 or 48 hours after the first dose of drug were shown between zanamivir and oseltamivir therapy (50.2% and 44.1%, at 24 h, or 86.7% and 83.1% at 48 h, respectively). For patients with influenza B, the percentage of patients afebrile at 24 hours or 48 hours after the first dose was significantly higher for patients treated with zanamivir than with oseltamivir (44.6% and 25.1% at 24 h, or 80.2% and 55.6% at 48 h, respectively; both P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Minor adverse reactions were observed in 18 patients treated with oseltamivir and in five patients with zanamivir. No severe adverse reactions were reported.
Treatment and Prophylaxis of Influenza				
Jefferson et al.[44] (2006) Neuraminidase inhibitors (NI) as prophylaxis and/or treatment for influenza or influenza-like illness (ILI) vs placebo	MA Individuals with known pre-existing chronic pathology known to aggravate the course of influenza	N=1,014 22-49 days	Primary: Efficacy (distribution and/or severity of influenza, numbers), viral load, adverse events	Primary: The use of NIs did not demonstrate an effect against ILI when used as prophylaxis when compared to placebo (RR 1.28, 95% CI: 0.45 to 3.66 for oseltamivir and RR 1.51, 95% CI: 0.77 to 2.95 for zanamivir). Against symptomatic influenza, the efficacy of oseltamivir was 61% (RR 0.39, 95% CI: 0.18 to 0.85) at the 75 mg dose and 73% (RR 0.27, 95% CI: 0.11 to 0.67) at the 150 mg dose. Zanamivir was calculated to be 62% efficacious (RR 0.38, 95% CI: 0.17 to 0.85). There was no significant effect from either NI on asymptomatic influenza. Nausea was associated with oseltamivir (OR 1.79, 95% CI: 1.10 to 2.93). In the treatment of postexposure prophylaxis, oseltamivir was found to have an efficacy rate of 58.5% (95% CI: 15.6% to 79.6%) for households and 68% (95% CI: 34.9% to 84.2%) to 89% in contacts of index cases; similar findings were reported for zanamivir. Results for alleviation of influenza symptoms favored the treatment groups (HR 1.33 [95% CI: 1.29 to 1.37] for zanamivir and 1.30 [95% CI: 1.13 to 1.50] for oseltamivir). Both NIs significantly diminished nasal titers. The use of oseltamivir was associated with lower respiratory tract complications (OR 0.32, 95% CI: 0.18 to 0.57).
Cooper et al.[45]	MA	N=>1,000	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2003) Neuraminidase inhibitors (NI) as prophylaxis and/or treatment for influenza vs placebo or standard care	Children, healthy adults, and adults at high risk	21-28 days	Duration of symptoms in days	In the intent-to treat-population with zanamivir, the median duration of symptoms in days was reduced by 1.0 (95% CI: 0.5 to 1.5) in the treatment of children, 0.8 (95% CI: 0.3 to 1.3) in otherwise healthy individuals, and 0.9 (95% CI: –0.1 to 1.9) for high risk individuals. In the intent-to-treat population with oseltamivir, the median duration of symptoms in days was reduced by 0.9 (95% CI: 0.3 to 1.5) in the treatment of children, 0.9 (95% CI: 0.3 to 1.4) in otherwise healthy individuals, and 0.4 (95% CI: –0.7 to 1.4) for high risk individuals. A relative reduction of 70%-90% in the odds of developing influenza was associated with the prophylactic use of zanamivir or oseltamivir. Some studies did not present the vaccination status of the individuals; for the ones that did, the percentage of patients vaccinated ranged from 0 % to 80%.
Matheson et al.[46] (2007) Neuraminidase inhibitors (NI) as prophylaxis and/or treatment for influenza vs placebo or other antiviral drugs	MA Healthy and at-risk children less than 12 years of age	N=1,500 Variable duration	Primary: Time to resolution of symptoms, secondary household attacks, confirmed influenza or influenza-like disease, adverse events	Primary: The median duration of illness was reduced by oseltamivir by 26% (36 hours) in healthy children with laboratory-confirmed influenza (P<0.0001). In comparison the reduction was only 7.7% (10 hours) in “at risk” (asthmatic) children (P=0.54). The median duration of illness was reduced by zanamivir by 24% (1.25 days) in healthy children with laboratory-confirmed influenza (P<0.001), and no information was available concerning “at risk” (asthmatic) children. A significant reduction in the complications of influenza (otitis media) was seen with oseltamivir, although a trend was seen with zanamivir. Vomiting was more common in children receiving placebo, while there was no difference between placebo and zanamivir in terms of adverse events.
Turner et al.[47] (2003)	MA Children, healthy	29 trials Duration	Primary: Median duration of symptoms, risk of	Primary: For influenza-positive patients, treatment with oseltamivir reduced the median duration of symptoms in the influenza positive group by 1.38

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Neuraminidase inhibitors (NI) as prophylaxis and/or treatment for influenza vs placebo	adults, and adults at high risk	varied up to 28 days	infection	days (95% CI: 0.80 to 1.96) for otherwise healthy adults; by 0.50 days (95% CI: –0.96 to 1.88) for the high-risk population, and by 1.5 days (95% CI: 0.8 to 2.2) for the group of children. Prophylaxis with oseltamivir resulted in a relative risk reduction of 75% to 90% depending on the strategy used and the patient population studied. For influenza-positive patients, treatment with zanamivir reduced the median duration of symptoms in the influenza positive group by 1.26 days (95% CI: 0.59 to 1.93) for otherwise healthy adults; by 1.99 days (95% CI: 0.90 to 3.08) for the high-risk population, and by 1.3 days (95% CI: 0.3 to 2.0) for the group of children. Prophylaxis with zanamivir resulted in a relative-risk reduction of 70% to 90% depending on the strategy used and the patient population studied.
Jefferson et al.[48] (2006) Amantadine, rimantadine, or neuraminidase inhibitors (NI) as prophylaxis and/or treatment for influenza vs placebo, no intervention, or symptomatic medication	MA Otherwise healthy individuals aged 16-65	52 trials Variable duration	Primary: Prophylactic efficacy, duration of nasal shedding, time to alleviate symptoms, adverse events, lower respiratory tract complications	Primary: For the prophylaxis of influenza A and influenza-like illness amantadine prevented 61% (95% CI: 35 to 76) and 25% (95% CI: 13 to 36) of cases respectively. The use of amantadine was associated with nausea (OR 2.56, 95% CI: 1.37 to 4.79), insomnia and hallucinations (2.54, 95% CI: 1.50 to 4.31). The duration of fever in days was significantly shortened with amantadine compared to placebo (0.99, 95% CI: -1.26 to -0.71), in comparison with nasal shedding of influenza A, no significant difference was seen (0.93, 95% CI: 0.71 to 1.21). Compared with placebo when used for prophylaxis, NI had no significant effect on influenza-like illness (1.28, 95% CI: 0.45 to 3.66 for oseltamivir 75 mg a day and 1.51, 95% CI: 0.77 to 2.95 for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				zanamivir 10 mg a day). Against symptomatic influenza, oseltamivir was 61% or 73% (75 mg and 150 mg doses) effective, while zanamivir was 62% efficacious. Nausea was associated with the use of oseltamivir (OR 1.79, 95% CI: 1.10 to 2.93). The protective efficacy of oseltamivir was 58.8% from household contacts and from 68% to 89% in contacts of index cases. Compared to placebo the HRs for the time-to-alleviate symptoms were 1.33 (95% CI: 1.29 to 1.37) for zanamivir and 1.30 (95% CI: 1.13 to 1.50) for oseltamivir, when the medications were started within 48 hours of onset of symptoms. In preventing lower respiratory tract complications in influenza cases, oseltamivir 150 mg a day was judged to be effective (OR 0.32, 95% CI: 0.18 to 0.57).

Study abbreviations: CI=confidence interval, DB=double blind, HR=hazard ratio, IC=index case, MA=meta analysis, MC=multicenter, OL=open label, OR=odds ratio, OS=observational study, PC=placebo controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk
Miscellaneous abbreviations: HIV=human immunodeficiency virus, ILI=influenza-like illness, LRTCs=lower respiratory tract complications, NI=neuraminidase inhibitors, PEP= postexposure prophylaxis, URTCs=upper respiratory tract complications
*Not commercially available in the US

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 9. Relative Cost of the Neuraminidase Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Oseltamivir	capsule, suspension	Tamiflu®	$$$-$$$$	N/A
Zanamivir	powder for oral inhalation	Relenza®	$$$	N/A

N/A=Not available

X. Conclusions

The neuraminidase inhibitors are approved for the treatment and prophylaxis of influenza A and influenza B virus infections. Guidelines recommend the use of either oseltamivir or zanamivir for the treatment and chemoprophylaxis of all influenza subtypes.[10-12] Due to the emergence of resistance, the adamantanes are not effective. Although rare, development of resistance to zanamivir and oseltamivir has been identified during treatment of seasonal influenza.[11]

Several clinical trials have demonstrated that the prophylactic use of oseltamivir and zanamivir reduces the risk of developing symptomatic influenza infections.[7,16-24] Studies have also shown the neuraminidase inhibitors reduce the duration and severity of illness, as well as complications compared to placebo.[26-35,38-42] There are relatively few studies that directly compare the efficacy and safety of oseltamivir and zanamivir. Guidelines do not give preference to one agent over another.[10-12]

Therefore, oseltamivir (Tamiflu®) and zanamivir (Relenza®) offer significant clinical advantages in general use over the other brands, generics and OTC products (if applicable).

XI. Recommendations

Oseltamivir (Tamiflu®) and zanamivir (Relenza®) are recommended for preferred status contingent upon statewide influenza epidemiology status as reported by the CDC.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Nucleosides and Nucleotides
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I. Overview

There are nearly 100 Herpesviridae known; however, only 8 human Herpesviruses (HHV) have been identified.[19] These eight viruses are classified into 3 subfamilies: alpha-herpesvirus which includes herpes simplex virus types 1 and 2 (HSV-1 and HSV-2, respectively) and varicella-zoster virus (VZV); beta-herpesvirus which includes cytomegalovirus (CMV) and roseolovirus; and gamma-herpesvirus which includes Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV).

The nucleosides and nucleotides are approved for the treatment of infections caused by HSV, VZV and CMV, as well as for the treatment of chronic hepatitis B, chronic hepatitis C, and respiratory syncytial virus.[1-14] They possess antiviral activity due to their structural similarity to the basic building blocks of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA).[17] Many of these agents inhibit viral DNA or RNA polymerase, the enzymes necessary for viral replication. In addition, these agents may also be incorporated into viral DNA during synthesis, acting as a chain terminator of DNA synthesis.

Infection with HSV is associated with chronic, life-long infections.[28] The two most common manifestations are genital herpes and labial herpes. Genital herpes typically results from infection with HSV-2; however, either HSV type can lead to genital ulcers.[28,37] Initial primary genital HSV infections tend to be more severe with lesions persisting for several weeks. Clinical manifestations include painful genital ulcers, itching, dysuria, headache, fever, malaise and lymphadenopathy.[18] Recurrent episodes are generally shorter and produce mainly localized vesicles which progress through ulcerated and crusted stages for up to 10 days. Labial herpes typically results from infection with HSV-1.[38] Initial primary episodes can be widespread and associated with severe discomfort; however, recurrent episodes tend to be more localized.[37] Before skin lesions appear, there is often a prodrome phase consisting of pain, itching, tingling and burning.[37-38] Papules then present on the lip and infrequently on the palate, chin or the oral mucosa. This is then followed by progression through ulcerated, crusted, and healing stages within five days (for recurrent episodes).[38]

Infection with VZV is a common cause of chickenpox in children and herpes zoster (shingles) in adults. Chickenpox is a highly contagious disease that is characterized by an exanthematous rash. Following resolution of the rash, the virus remains dormant in the dorsal root ganglia until reactivation, which then causes herpes zoster. The factors that lead to reactivation are unknown; however, the elderly and immunocompromised are most often affected. Herpes zoster is characterized by a unilateral painful skin rash with vesicular eruptions. It is also associated with acute neuritis and postherpetic neuralgia. There are vaccines that are currently available for the prevention of chickenpox and herpes zoster.

CMV is a common virus that infects most people worldwide. Immunocompetent individuals are often asymptomatic; however CMV may cause severe disease in immunocompromised individuals, including pneumonia, retinitis, hepatitis, gastritis, colitis, Guillain-Barre syndrome, myocarditis, thrombocytopenia, hemolytic anemia, and meningoencephalitis.[22]

The hepatitis B virus (HBV) is a DNA virus that is transmitted through exposure with infected blood and body fluids, and is a leading cause of death from liver disease.[23-24] Acute infection occurs following HBV exposure and the infection generally clears after 1-3 months in immunocompetent individuals. However, chronic infections (≥6 months) are increased in immunocompromised patients and patients who are exposed early in life.[24] The hepatitis C virus (HCV) is a RNA virus that is also transmitted through exposure with infected blood.[25-26] Once infected, HCV causes hepatic inflammation and steatosis.[25]With persistent infections, patients may develop hepatic fibrosis, which can lead to cirrhosis and an increased risk for hepatocellular carcinoma. There are six genotypes of HCV; type 1 genotype is the most prevalent in the U.S.[25] There are differences in response to therapy among the genotypes.[26] Type 1 genotype is associated with a lower response to therapy.[26] Thus, a longer duration of therapy is recommended for patients infected with HCV genotype 1.

RSV is the leading cause of lower respiratory tract infections in children. Nearly all children will be infected with RSV by age two. In most patients, RSV infection will cause a low-grade fever, cough and wheezing that resolves after several days and only requires symptomatic treatment. In high-risk patients, such as those with chronic lung disease, those born premature and those with congenital heart disease, RSV exposure may lead to more severe symptoms such as hypoxemia and cyanosis, and may necessitate hospitalization.

Several of the nucleoside and nucleotide analogues have been modified and formulated into prodrugs to improve their pharmacokinetic profile. Valacyclovir and valganciclovir are the L-valyl ester of acyclovir and ganciclovir, respectively.[3,13-14] These modifications increase the bioavailability of the parent compound. Famciclovir is a diacetyl ester of penciclovir, which is an antiviral agent that is only used topically due to its low bioavailability. To obtain the therapeutic effect of penciclovir, famciclovir must be orally administered and metabolized to penciclovir.

The nucleosides and nucleotides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Acyclovir, famciclovir, ganciclovir, ribavirin, and valacyclovir are available in a generic formulation. This class was last reviewed in November 2009.

Table 1. Nucleosides and Nucleotides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Acyclovir	capsule, injection, suspension, tablet	Zovirax®*	acyclovir
Adefovir	tablet	Hepsera®	none
Cidofovir	injection	Vistide®	none
Entecavir	solution, tablet	Baraclude®	none
Famciclovir	tablet	Famvir®*	famciclovir
Ganciclovir	injection	Cytovene®*	ganciclovir
Ribavirin	capsule, inhalation solution, solution, tablet	Copegus®*, Rebetol®*, Virazole®	ribavirin
Telbivudine	tablet	Tyzeka®	none
Valacyclovir	tablet	Valtrex®*	valacyclovir
Valganciclovir	solution, tablet	Valcyte®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the nucleosides and nucleotides are summarized in Table 2.

Table 2. Treatment Guidelines Using the Nucleosides and Nucleotides

Clinical Guideline	Recommendation(s)

Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines: Management of Encephalitis[70] (2008)**	• Herpes simplex virus
	  ○ Acyclovir is recommended
	• Varicella-zoster virus
	  ○ Acyclovir is recommended
	  ○ Ganciclovir can be considered an alternative
	  ○ Adjunctive corticosteroids can be considered
	• Cytomegalovirus
	  ○ The combination of ganciclovir plus foscarnet is recommended
	  ○ Cidofovir is not recommended because its ability to penetrate the blood-brain barrier has been poorly studied.
	• Human herpesvirus 6
	  ○ Ganciclovir or foscarnet should be used in

Clinical Guideline	Recommendation(s)

	immunocompromised patients
	  ○ Use of these agents in immunocompetent patients can be considered, but there are not good data on their effectiveness.
	• B virus
	  ○ Valacyclovir is recommended
	  ○ Alternative agents are ganciclovir and acyclovir
	• Measles virus
	  ○ Ribavirin can be considered
	  ○ Intrathecal ribavirin can be considered in patients with subacute sclerosing panencephalitis.
	• Nipah virus
	  ○ Ribavirin can be considered

American Association for the Study of Liver Diseases (AASLD): **Chronic Hepatitis B Update**[34] **(2009)**	<u>General Information</u>
	• The aims of treatment of chronic hepatitis B are to achieve sustained suppression of HBV replication and remission of liver disease. The ultimate goal is to prevent cirrhosis, hepatic failure and hepatocellular carcinoma.
	• Parameters used to assess treatment response include normalization of serum ALT, decrease in serum HBV DNA level, loss of hepatitis B e antigen (HBeAg) with or without detection of anti-HBe, and improvement in liver histology.
	• Responses to antiviral therapy of chronic hepatitis B are categorized as biochemical (BR), virologic (VR), or histologic (HR), and as on-therapy or sustained off therapy.
	• Seven therapeutic agents have been approved for the treatment of adults with chronic hepatitis B in the United States. While interferons are administered for predefined durations, the nucleoside/nucleotide analogues are usually administered until specific endpoints are achieved. The difference in approach is related to the additional immune modulatory effects of the interferons.
	<u>General Treatment Recommendations</u>
	• Patients with HBeAg-positive chronic hepatitis B with ALT >2 times normal or moderate/severe hepatitis on biopsy and HBV DNA >20,000 IU/mL should be considered for treatment.
	  ○ Treatment should be delayed for 3 to 6 months in persons with compensated liver disease to determine if spontaneous HBeAg seroconversion occurs.
	  ○ Patients with icteric ALT flares should be promptly treated.
	  ○ Treatment may be initiated with any of the 7 approved antiviral medications, but peginterferon alfa, tenofovir or entecavir are preferred.
	• Patients with HBeAg-positive chronic hepatitis B and ALT persistently normal or minimally elevated (<2 times normal) generally should not be initiated on treatment.
	• Children with elevated ALT >2 times normal should be considered for treatment if ALT levels remain elevated at this level for longer than 6 months.
	  ○ Treatment may be initiated with interferon alfa or lamivudine.
	• Patients with HBeAg-negative chronic hepatitis B (serum HBV DNA >20,000 IU/mL and elevated ALT>2 times normal) should be considered for treatment.
	  ○ Liver biopsy may be considered for HBeAg-negative patients with lower HBV DNA levels (2,000-20,000 IU/mL) and borderline normal or minimally elevated ALT levels.
	  ○ Treatment may be initiated if there is moderate/severe

Clinical Guideline	Recommendation(s)
	inflammation or significant fibrosis on biopsy. o Treatment may be initiated with any of the 7 approved antiviral medications, but peginterferon alfa, tenofovir or entecavir are preferred in view of the need for long-term treatment. • Patients who failed to respond to prior interferon alfa (standard or pegylated) therapy may be retreated with nucleoside/nucleotide analogues (NA). • Patients who failed to achieve primary response as evidenced by <2 log decrease in serum HBV DNA level after at least 6 months of NA therapy should be switched to an alternative treatment or receive additional treatment. • In patients with inactive HBsAg carrier state, antiviral treatment is not indicated, but these patients should be monitored. <u>Antiviral Resistance</u> • A major concern with long-term NA treatment is the selection of antiviral-resistant mutations. The rate at which resistant mutants are selected is related to pretreatment serum HBV DNA level, rapidity of viral suppression, duration of treatment, and prior exposure to NA therapies. • Among the approved NA therapies for hepatitis B, lamivudine is associated with the highest and entecavir and tenofovir with the lowest rates of drug resistance in NA-naïve patients. • Another potential consequence of antiviral-resistant mutations is cross-resistance with other NAs, thus limiting future treatment options. • Recently, there have also been reports of multi-drug resistant mutants in patients who have received sequential NA monotherapy. • Judicious use of NA in patients with chronic hepatitis B is the most effective prophylaxis against the development of antiviral-resistant HBV. • Patients with minimal disease and those who are unlikely to achieve sustained response should not be treated with NA, particularly if they are young (<30 years). • When possible, the most potent NA with the lowest rate of genotypic resistance should be administered and compliance reinforced. • Although combination therapy has been shown to prevent antiviral resistance in patients with HIV infection, the promise of combination therapy has not yet been fulfilled for patients with HBV infection. • Once antiviral-resistant HBV mutants have been selected, they are archived (retained in the virus population) even if treatment is stopped and lamivudine-resistant HBV mutants had been detected up to four years after withdrawal of lamivudine. <u>Patients Who Develop Breakthrough Infection While Receiving NA Therapy</u> • All patients with virologic breakthrough should be considered for rescue therapy. • For patients in whom there was no clear indication for hepatitis B treatment and who continue to have compensated liver disease, withdrawal of therapy may be considered but these patients need to be closely monitored and treatment reinitiated if they experience severe hepatitis flares. <u>Treatment of Patients with Lamivudine (or telbivudine)-resistant HBV</u> • If adefovir is used, lamivudine (or telbivudine) should be continued indefinitely to decrease the risk of hepatitis flares during the transition period and to reduce the risk of subsequent adefovir resistance.

Clinical Guideline	Recommendation(s)
	• If tenofovir is used, continuation of lamivudine (or telbivudine) is recommended to decrease the risk of subsequent antiviral resistance. • If entecavir is used, lamivudine or telbivudine should be stopped as continued presence of lamivudine- (or telbivudine-) resistant mutations will increase the risk of entecavir resistance. Entecavir is not an optimal therapy because of increasing risk of resistance to entecavir over time. <u>Treatment of Patients with Adefovir-resistant HBV</u> • In patients with no prior exposure to other NA, lamivudine, telbivudine or entecavir may be added. Alternatively, adefovir may be stopped and tenofovir plus lamivudine or emtricitabine may be used. • In patients with prior lamivudine resistance in whom lamivudine had been stopped when treatment was switched to adefovir, adefovir may be stopped and tenofovir plus lamivudine, emtricitabine or entecavir may be used but the durability of response to this combination is unknown. <u>Treatment of Patients with Entecavir-resistant HBV</u> • Adefovir or tenofovir can be used as it has been shown to have activity against entecavir-resistant HBV in *in vitro* studies, but clinical data are lacking. <u>Treatment of Patients with Compensated Cirrhosis</u> • Treatment should be considered for patients with ALT >2 times normal, and for patients with normal or minimally elevated ALT if serum HBV DNA levels are high (>2,000 IU/mL). • Patients with compensated cirrhosis are best treated with NAs because of the risk of hepatic decompensation associated with interferon alfa–related flares of hepatitis. In view of the need for long-term therapy, tenofovir or entecavir is preferred. <u>Treatment of Patients with Decompensated Cirrhosis</u> • Treatment should be promptly initiated with a NA that can produce rapid viral suppression with low risk of drug resistance. • Lamivudine or telbivudine may be used as initial treatment in combination with adefovir or tenofovir to reduce the risk of drug resistance. • Entecavir or tenofovir alone would be an appropriate treatment in this setting but clinical data documenting their safety and efficacy in patients with decompensated cirrhosis are lacking. • Treatment should be coordinated with a transplant center. • Interferon alfa or peginterferon alfa should not be used in patients with decompensated cirrhosis. <u>Treatment Duration</u> • The recommended treatment duration for HBeAg-positive chronic hepatitis B is 16 weeks for standard interferon alfa and 48 weeks for peginterferon alfa. • The recommended treatment duration for HBeAg-negative chronic hepatitis B is 48 weeks for both standard and peginterferon alfa. • Treatment with NAs should be continued until the patient has achieved HBeAg seroconversion and undetectable serum HBV (for patients with HBeAg-positive chronic hepatitis B). For patients with HBeAg-negative chronic hepatitis B, treatment should be continued until the patient has achieved HBsAg clearance. For patients with compensated cirrhosis, treatment should be received long-term. However, treatment may be stopped in HBeAg-positive patients if they have confirmed HBeAg seroconversion and have completed at least 6 months of consolidation therapy and in HBeAg-negative patients if they have

Clinical Guideline	Recommendation(s)
	confirmed HBsAg clearance. For patients with decompensated cirrhosis and recurrent hepatitis B post–liver transplantation, life-long treatment is recommended. Recommendations for Treatment of Patients with HBV/HIV Coinfection • Patients who meet criteria for chronic hepatitis B should be treated. • Patients who are not on HAART and are not anticipated to require HAART in the near future should be treated with an antiviral therapy that does not target HIV, such as peginterferon alfa or adefovir. Although telbivudine does not target HIV, it should not be used in this circumstance. • Patients in whom treatment for both HBV and HIV is planned should receive therapies that are effective against both viruses: lamivudine plus tenofovir or emtricitabine plus tenofovir are preferred. • Patients who are already on effective HAART that does not include a drug active against HBV may be treated with peginterferon alfa or adefovir. • In patients with lamivudine resistance, tenofovir should be added. Recommendations for Treatment of Hepatitis B Carriers Who Require Immunosuppressive or Cytotoxic Therapy • Prophylactic antiviral therapy is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy. • Patients with baseline HBV DNA<2,000 IU/mL level should continue treatment for 6 months after completion of chemotherapy or immunosuppressive therapy. • Patients with high baseline HBV DNA (>2,000 IU/mL) level should continue treatment until they reach treatment endpoints as in immunocompetent patients. • Lamivudine or telbivudine can be used if the anticipated duration of treatment is short (<12 months) and baseline serum HBV DNA is not detectable. • Tenofovir or entecavir is preferred if longer duration of treatment is anticipated. • Interferon alfa should be avoided in view of the bone marrow suppressive effect. Recommendations for Treatment of Patients with Acute Symptomatic Hepatitis B • Treatment is only indicated for patients with fulminant hepatitis B and those with protracted, severe acute hepatitis B. • Lamivudine or telbivudine may be used when the anticipated duration of treatment is short; otherwise, entecavir is preferred. • Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation. • Interferon alfa therapy is contraindicated.
American Association for the Study of Liver Diseases (AASLD): **Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection**[16] **(2011)**	General Considerations • The optimal therapy for genotype 1, chronic HCV infection is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin. • Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin. Treatment-Naive Patients: • The recommended dose of boceprevir is 800 mg administered with food three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 24-44 weeks preceded by 4 weeks of lead-in treatment with peginterferon alfa and ribavirin alone.

Clinical Guideline	Recommendation(s)
	• Patients without cirrhosis treated with boceprevir, peginterferon, and ribavirin, preceded by 4 weeks of lead-in peginterferon and ribavirin, whose HCV RNA level at weeks 8 and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (4 weeks lead-in with peginterferon and ribavirin followed by 24 weeks of triple therapy). • Treatment with all three drugs (boceprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24. • The recommended dose of telaprevir is 750 mg administered with food (not low-fat) three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12-36 weeks of peginterferon alfa and ribavirin. • Patients without cirrhosis treated with telaprevir, peginterferon, and ribavirin, whose HCV RNA level at weeks 4 and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks. • Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peginterferon and ribavirin should receive therapy for a duration of 48 weeks. • Treatment with all three drugs (telaprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >1,000 IU/mL at treatment weeks 4 or 12 and/or detectable at treatment week 24. <u>Treatment-Experienced Patients</u> • Re-treatment with boceprevir or telaprevir, together with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin. • Re-treatment with telaprevir, together with peginterferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peginterferon alfa and/or weight-based ribavirin. • Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers, may be considered for partial responders, but cannot be recommended for null responders. • Patients re-treated with boceprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. • Patients re-treated with telaprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 1,000 IU at weeks 4 or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. • Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose. • Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (>1 log increase in serum HCV RNA above nadir) is observed. • Patients who fail to have a virological response, who experience virological breakthrough, or who relapse on one protease inhibitor should not be re-treated with the other protease inhibitor.
American Association for the Study of Liver Diseases	<u>General Information</u> • The goal of therapy is to prevent complications and death from HCV

Clinical Guideline	Recommendation(s)
(AASLD): **Diagnosis, Management, and Treatment of Hepatitis C: Update[36] (2009)**	infection. Treatment responses are defined by a surrogate virological parameter rather than a clinical endpoint. Short-term outcomes can be measured biochemically (normalization of serum ALT levels), virologicaly (absence of HCV RNA from serum by a sensitive PCR-based assay), and histologically (point improvement in necroinflammatory score with no worsening in fibrosis score). • Several types of virological responses may occur, labeled according to their timing relative to treatment. The most important is the sustained virological response (SVR), defined as the absence of HCV RNA from serum by a sensitive PCR assay 24 weeks following discontinuation of therapy (virological cure). Undetectable virus at the end of either a 24-week or 48-week course of therapy is referred to as an end-of-treatment response (ETR). An ETR does not accurately predict that an SVR will be achieved, but is necessary for it to occur. • The currently recommended therapy of chronic HCV infection is the combination of a pegylated interferon alfa and ribavirin. • Treatment decisions should be individualized based on the severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions, and the patient's readiness for treatment. <u>Genotype1 and Genotype 4 HCV Infection</u> • Treatment with peginterferon plus ribavirin should be planned for 48 weeks. • Treatment may be discontinued in patients who do not achieve an early virological response (EVR; >2 log reduction in HCV RNA at week 12 of treatment). • Patients who do not achieve a complete EVR (undetectable HCV RNA at week 12 of treatment) should be re-tested at week 24, and if HCV RNA remains positive, treatment should be discontinued. • For patients with genotype 1 infection who have delayed virus clearance (HCV RNA test becomes negative between weeks 12 and 24), consideration should be given to extending therapy to 72 weeks. <u>Genotype 2 or Genotype 3 HCV Infection</u> • Treatment with peginterferon plus ribavirin should be administered for 24 weeks. <u>Retreatment</u> • Retreatment with peginterferon plus ribavirin in patients who did not achieve an SVR after a prior full course of peginterferon plus ribavirin is not recommended, even if a different type of peginterferon is administered. • Retreatment with peginterferon plus ribavirin can be considered for non-responders or relapsers who have previously been treated with non-pegylated interferon with or without ribavirin, or with peginterferon monotherapy, particularly if they have bridging fibrosis or cirrhosis. • Maintenance therapy is not recommended for patients with bridging fibrosis or cirrhosis who have failed a prior course of peginterferon and ribavirin. <u>Treatment of Persons with Normal Serum Aminotransferase Values</u> • Regardless of the serum alanine aminotransferase level, the decision to initiate therapy with pegylated interferon and ribavirin should be individualized based on the severity of liver disease by liver biopsy, the potential for serious side effects, the likelihood of response, and the presence of comorbid conditions. • The treatment regimen for HCV-infected persons with normal

Clinical Guideline	Recommendation(s)
	aminotransferase levels should be the same as that used for persons with elevated serum aminotransferase levels. Treatment of Children • Children aged 2-17 years who are infected with HCV should be considered appropriate candidates for treatment using the same criteria as that used for adults. • Children should be treated with pegylated interferon alfa-2b, 60 mcg/m^2 weekly in combination with ribavirin, 15 mg/kg daily for a duration of 48 weeks. Treatment of HIV-infected Persons • Hepatitis C should be treated in the HIV/HCV co-infected patient in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of morbidity from the adverse effects of therapy. • Initial treatment of hepatitis C in most HIV-infected patients should be peginterferon alfa plus ribavirin for 48 weeks at doses recommended for HCV mono-infected patients. • When possible, patients receiving zidovudine (AZT) and especially didanosine (ddI) should be switched to an equivalent antiretroviral agent before beginning therapy with ribavirin. • HIV-infected patients with decompensated liver disease (CTP Class B or C) should not be treated with peginterferon alfa and ribavirin and may be candidates for liver transplantation.

American Gastroenterological Association (AGA): **Medical Position Statement on the Management of Hepatitis C[35] (2006)**	• Therapy is indicated for previously untreated patients with chronic hepatitis C, circulating HCV RNA, elevated aminotransferase levels, evidence on liver biopsy of moderate to severe hepatitis grade and stage, and compensated liver disease.
	• Patients with normal ALT activity are candidates for antiviral therapy or for monitoring without intervention, as determined on an individual basis and as influenced by patient factors such as motivation, genotype, histologic activity, and fibrosis.
	• Patients with compensated cirrhosis who can tolerate therapy are candidates for treatment.
	• The treatment of choice is pegylated interferon alfa plus ribavirin.
	• Patients with genotypes 1 and 4 require 48 weeks of therapy with pegylated interferon and high daily doses of ribavirin (1,000–1,200 mg, depending on weight).
	• Patients with genotypes 2 and 3 can be treated for only 24 weeks with pegylated interferon and with 800 mg of ribavirin daily, with the following exceptions:
	  ○ A longer duration of therapy may be considered on an individual patient basis taking into account factors such as elevated viral level, cirrhosis, or delayed response to therapy.
	  ○ 12 weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week 4.
	  ○ Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks.
	• Therapy with peginterferon alfa and ribavirin should be strongly considered for patients who experienced a relapse after a course of standard interferon alfa/ribavirin combination therapy, while a longer duration of therapy in patients who experienced a relapse after 12 months of treatment with peginterferon alfa plus ribavirin is of unproven efficacy.
	• For children, the general principles of management are the same as

Clinical Guideline	Recommendation(s)
	those for adults, except that treatment is not recommended for children younger than 3 years. • For HIV-infected individuals, the optimal therapy consists of peginterferon alfa plus ribavirin for 48 weeks, regardless of genotype. Because of potential drug-drug interactions in patients on HIV treatment regimens that include didanosine, HIV regimens should be altered in those starting combination therapy for HCV infection. If didanosine is critical to the HIV regimen, ribavirin should be avoided.

Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines[28] (2010)**	<u>Genital Herpes Infection</u>
	• The use of systemic antivirals including valacyclovir, acyclovir, and famciclovir is encouraged for the treatment of primary and recurrent genital herpes. Topical therapy with antiviral drugs offers minimal clinical benefit, and their use is not recommended.
	• Systemic antiviral drugs partially control the symptoms and signs of herpes infection when used to treat first clinical episodes and recurrent episodes, or when used as daily suppressive therapy.
	• Recommended regimens for initial clinical episodes include:
	  o Acyclovir 400 mg three times a day for 7–10 days or 200 mg five times a day for 7–10 days
	  o Famciclovir 250 mg three times a day for 7–10 days
	  o Valacyclovir 1 g twice a day for 7–10 days
	• Recommended regimens for suppressive therapy in recurrent herpes (≥6 episodes/year) include:
	  o Acyclovir 400 mg twice daily
	  o Famciclovir 250 mg twice daily
	  o Valacyclovir 500 mg once daily or 1,000 g once daily
	• Recommended regimens for episodic therapy in recurrent herpes include:
	  o Acyclovir 400 mg three times a day for 5 days or 800 mg twice a day for 5 days or 800 mg three times a day for 2 days
	  o Famciclovir 125 mg twice a day for 5 days or 1 g twice a day for 1 day or 500 mg once then 250 mg twice a day for 2 days
	  o Valacyclovir 500 mg twice a day for 3 days or 1 g once a day for 5 days
	• Recommended regimen for severe infections include:
	  o Intravenous acyclovir 5–10 mg/kg every 8 hours for 2–7 days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days of total therapy.
	• Recommended regimens for suppressive therapy in patients with HIV include:
	  o Acyclovir 400-800 mg twice to three times daily
	  o Famciclovir 500 mg twice daily
	  o Valacyclovir 500 mg twice daily
	• Recommended regimens for episodic therapy in patients with HIV include:
	  o Acyclovir 400 mg three times daily for 5-10 days
	  o Famciclovir 500 mg twice daily for 5-10 days
	  o Valacyclovir 1 g twice daily for 5-10 days
	<u>Hepatitis B</u>
	• No specific therapy is available for persons with acute hepatitis B; treatment is supportive.
	• Persons with chronic hepatitis B virus (HBV) infection should be referred for evaluation to a physician experienced in the management of chronic liver disease (CLD).
	• Therapeutic agents approved by FDA for treatment of chronic hepatitis

Clinical Guideline	Recommendation(s)
	B can achieve sustained suppression of HBV replication and remission of liver disease in some persons. Hepatitis C • Combination therapy with pegylated interferon and ribavirin is the treatment of choice for patients with chronic hepatitis C.
American College of Obstetricians and Gynecologists (ACOG): **Herpes Simplex Virus Infections**[30] **(2004)**	• Acyclovir, valacyclovir, and famciclovir are antiviral drugs approved for treatment of genital herpes. • Comparative trials of these medications suggest they have compatible clinical efficacy and result in comparable decrease in viral shedding. • Treatment should be offered for first episode, even if they appear to be mild initially. • Treatment of first episodes decreases lesions, viral shedding, and symptoms, but does not affect the long-term natural history of infection. • Newly acquired HSV infections can have a prolonged course, with systemic and neurologic involvement that can be substantially ameliorated by using antiviral therapy. Oral therapy is recommended, except in severe cases in which a woman is unable to tolerate oral intake or has prominent neurologic involvement. Such patients should be hospitalized and treated with intravenous acyclovir. • Recurrent episodes of genital herpes can be managed effectively either with daily suppressive or episodic antiviral drugs. • Episodic therapy decreases the duration of the episode (lesion, pain, and viral shedding) and is most effective when the patient initiates the therapy at prodrome or at the beginning of the episode. This form of therapy is most effective for a patient with infrequent symptomatic recurrences. • Topical antiviral medication is not effective therapy and does not add to the benefit of the oral medication; its use is discouraged.
World Health Organization (WHO): **Guidelines for the Management of Sexually Transmitted Infections**[29] **(2003)**	Genital Herpes Infection • The first clinical episode should be treated with acyclovir, valacyclovir, or famciclovir, all for 7 days. • Recurrent infections should be treated with acyclovir, valacyclovir, or famciclovir, all for 5 days. • Suppressive therapy may include acyclovir, valacyclovir, or famciclovir continuously. • Severe disease should be treated with IV acyclovir. • Treatment during pregnancy should be with acyclovir. • Patients who are co-infected with HIV should be treated with acyclovir. • Neonates should be treated with IV acyclovir.
Centers for Disease Control and Prevention (CDC): **Prevention of Herpes Zoster – Recommendations of the Advisory Committee on Immunization Practices (ACIP)**[79] **(2008)**	Vaccination • Zoster vaccine is recommended for all persons aged ≥60 years who have no contraindications, including persons who report a previous episode of zoster or who have chronic medical conditions. Zoster vaccination is not indicated to treat acute zoster, to prevent persons with acute zoster from developing postherpetic neuralgia (PHN), or to treat ongoing PHN. Treatment • Acyclovir, famciclovir, and valacyclovir are approved by the FDA for treatment of zoster in immunocompetent patients. All three are nucleoside analogs that inhibit replication of human herpes viruses, including VZV. • Clinical trials have indicated that acyclovir, famciclovir, and valacyclovir reduce the duration of viral shedding and lesion

Clinical Guideline	Recommendation(s)

	formation, reduce the time to rash healing, and decrease the severity and duration of acute pain from zoster and the risk for progression to PHN.
	• Because all three antiviral agents are safe and well tolerated, many experts recommend that treatment should be considered for all eligible patients with zoster, and specifically recommend treatment for persons:
	  o Aged ≥50 years
	  o Moderate or severe pain
	  o Moderate or severe rash
	  o Involvement of non-truncal dermatomes
	• In clinical trials, treatment has been initiated within 72 hours of rash onset, a biologically arbitrary time point that often is not feasible in clinical practice. The benefits of later treatment have not been studied. If treatment cannot be initiated within 72 hours of rash onset, experts recommend that it should be initiated as soon as possible, particularly in the presence of new vesicle formation or of complications.

Infectious Diseases Society of America (IDSA):
Recommendations for the Management of Herpes Zoster[85]
(2007)
	• Topical antiviral therapy lacks efficacy in patients with herpes zoster (HZ) and is not recommended.
	• Systemic antiviral therapy is strongly recommended as first-line treatment for all immunocompetent patients with HZ who fulfill any of the following criteria:
	  o >50 years of age
	  o Moderate or severe pain
	  o Moderate or severe rash
	  o Non-truncal involvement
	• In patients who have a low risk for complications of HZ (those who are younger with mild acute pain and rash and truncal involvement) the potential benefits of treatment are unknown but may be meaningful because such patients can still develop postherpetic neuralgia (PHN).
	• Antiviral therapy should be considered even for patients whose risk of developing PHN and other complications of HZ is likely to be low.
	• There are no systematic data addressing the effectiveness of antiviral therapy administered outside of the clinical trial setting. In clinical practice, brivudine, famciclovir, and valacyclovir can be expected to have greater overall effectiveness than acyclovir on the basis of their potentially greater efficacy and higher and more reliable levels of antiviral activity in blood.
	• In patients presenting >72 h after rash onset, the potential benefits of initiating antiviral therapy are unknown but might be meaningful, given the minimal risks of treatment with acyclovir, famciclovir, and valacyclovir.
	• The initiation of antiviral therapy can be considered for patients presenting >72 hours after rash onset with continued new vesicle formation or when there are cutaneous, motor, neurologic, or ocular complications. Advanced age and severe pain (which are potent risk factors for PHN) are additional factors that can prompt consideration of initiating antiviral therapy >72 h after rash onset.
	• In patients who still have new vesicles forming or who have cutaneous, motor, neurologic, or ocular complications after 7 days of antiviral therapy, it is recommended that consideration be given to extending the duration of antiviral therapy for >7 days for these patients.
	• When rash healing has not occurred in a normal fashion in an immunocompetent patient with HZ, further evaluation by an infectious diseases specialist is recommended. Infection with varicella zoster virus (VZV) resistant to acyclovir (mediated by absent or altered

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	expression of thymidine kinase) has been reported in immunocompromised but not in immunocompetent patients.
American Academy of Pediatrics (AAP): **Varicella-Zoster Infections**[31] **(2009)**	• The decision to use antiviral therapy and the route and duration of therapy should be determined by specific host factors, extent of infection, and initial response to therapy. • Antiviral drugs have a limited window of opportunity to affect the outcome of VZV infection. In immunocompetent hosts, most virus replication has stopped by 72 hours after onset of rash; the duration of replication may be extended in immunocompromised hosts. • Oral acyclovir is not recommended for routine use in otherwise healthy children with varicella. Administration within 24 hours of onset of rash results in only a modest decrease in symptoms. • Oral acyclovir should be considered for otherwise healthy people at increased risk of moderate to severe varicella, such as people older than 12 years of age, people with chronic cutaneous or pulmonary disorders, people receiving long-term salicylate therapy, and people receiving short, intermittent, or aerosolized courses of corticosteroids. • Some experts also recommend use of oral acyclovir for secondary household cases in which the disease usually is more severe than in the primary case. • Intravenous antiviral therapy is recommended for immunocompromised patients, including patients being treated with chronic corticosteroids. Therapy initiated early in the course of the illness, especially within 24 hours of rash onset, maximizes efficacy. Oral acyclovir should not be used to treat immunocompromised children with varicella because of poor oral bioavailability. Some experts have used high-dose oral acyclovir, valacyclovir, or famciclovir in selected immunocompromised patients perceived to be at lower risk of developing severe varicella, such as HIV-infected patients with relatively normal concentrations of CD4+ T-lymphocytes and children with leukemia in whom careful follow-up is ensured. • Famciclovir is converted to penciclovir, which has an extended half-life in infected cells. Valacyclovir is converted to acyclovir and produces fourfold greater serum concentrations than those produced by oral acyclovir. No pediatric formulation is available for either medication, and insufficient data exist on the use or dose of these drugs in children to support therapeutic recommendations.
American Academy of Pediatrics (AAP): **Respiratory Syncytial Virus**[33] **(2009)**	• Primary treatment is supportive and should include hydration, careful clinical assessment of respiratory status, including measurement of oxygen saturation, use of supplemental oxygen, suction of the upper airway, and if necessary, intubation and mechanical ventilation. • Ribavirin has in vitro antiviral activity against respiratory syncytial virus (RSV), and aerosolized ribavirin therapy has been associated with a small but statistically significant increase in oxygen saturation during the acute infection in several small studies. However, a consistent decrease in need for mechanical ventilation, decrease in length of stay in the pediatric intensive care unit, or reduction in days of hospitalization among ribavirin recipients has not been demonstrated. • The aerosol route of administration, concern about potential toxic effects among exposed health care professionals, and conflicting results of efficacy trials have led to decreasing use of this drug. • Ribavirin is not recommended for routine use but may be considered for use in select patients with documented, potentially life-threatening RSV infection.
Centers for Disease Control and	<u>Prevention of Cytomegalovirus</u>

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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[32] (2008)**	• CMV end-organ disease is best prevented by using antiretroviral therapy (ART) to maintain the CD4+ count >100 cells/µL. • Although oral valganciclovir would likely prevent the occurrence of CMV retinitis in patients with CD4+ counts <50 cells/µL, such therapy is not generally recommended because of the potential to induce CMV resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage. <u>Treatment of Cytomegalovirus Disease</u> • Oral valganciclovir, IV ganciclovir, IV ganciclovir followed by oral valganciclovir, IV foscarnet, IV cidofovir, and the ganciclovir intraocular implant coupled with valganciclovir are all effective treatments for CMV retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, IV, and local options. • The choice of initial therapy for CMV retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in terms of protecting vision, and thus clinical judgment must be used when choosing a regimen. • The ganciclovir intraocular implant plus oral valganciclovir is more effective than once-daily IV ganciclovir (and presumably to once-daily oral valganciclovir) for preventing relapse of retinitis. For this reason, many HIV specialists recommend the intraocular implant plus valganciclovir as the preferred initial therapy for patients with immediately sight threatening lesions (adjacent to the optic nerve or fovea); for patients with small peripheral lesions oral valganciclovir alone may be adequate. Many ophthalmologists recommend an initial intravitreous injection of ganciclovir at the time of diagnosis of CMV retinitis to deliver a high local concentration of ganciclovir to the eye immediately, until the ganciclovir implant can be placed. • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) is recommended for life, unless immune reconstitution occurs as a result of ART. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir or valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, parenteral cidofovir, and (for retinitis only) ganciclovir administration through intraocular implant. <u>Treatment of Herpes Simplex Virus Disease</u> • Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for 5–10 days. • Severe mucocutaneous HSV lesions are best treated initially with IV acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed. • Genital HSV infection should be treated with oral valacyclovir, famciclovir, or acyclovir for 5–14 days. Short-course therapy (1, 2, or 3 days) should not be used in patients with HIV infection. • Most recurrences of genital herpes can be prevented by use of daily anti-HSV therapy, and this is recommended for persons who have frequent or severe recurrences. • Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is

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	effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in HIV-infected persons or twice-daily regimens with acyclovir or famciclovir should be used.
	Treatment of Varicella Zoster Virus Disease
	• For uncomplicated varicella, recommended treatment options are oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily), valacyclovir (1 g PO TID), or famciclovir (500 mg PO TID) for 5–7 days.
	• IV acyclovir for 7–10 days is the recommended initial treatment for HIV-infected patients with severe chickenpox. If there is no evidence of visceral involvement with VZV, switching to oral antiviral therapy after the patient has defervesced may be permissible.
	• The recommended treatment options for acute localized dermatomal herpes zoster in HIV-infected patients are oral valacyclovir, famciclovir, or acyclovir for 7–10 days, although longer durations of therapy should be considered if lesions are slow to resolve. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule.
	• If cutaneous lesions are extensive or if visceral involvement is suspected, IV acyclovir should be initiated and continued until clinical improvement is evident. A switch from IV acyclovir to oral antiviral therapy (to complete a 10–14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral VZV infection are clearly improving.
	Treatment of Hepatitis B Virus Coinfection in Patients Not Receiving Antiretroviral Therapy
	• For patients with CD4+ counts >350 cells/µL who are not receiving ART but meet criteria for HBV treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of HBV DNA levels and follow-up to evaluate for HBeAg seroconversion. However, early initiation of ART should also be considered for HIV/HBV-co-infected persons with CD4+ counts >350 cells/µL.
	Treatment of Hepatitis B Virus Coinfection in Patients Who Require Antiretroviral Therapy
	• For HIV-infected persons, some experts recommend combination therapy with two agents active against HBV to reduce the risk of HBV drug resistance, although there are no results from controlled trials as yet to support this strategy.
	• Among patients infected with HBV, HCV, and HIV, consideration of the need for ART should be the first priority. If ART is not required, interferon-based therapy, which suppresses both HCV and HBV, should be considered. If interferon-based therapy for HCV has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended.
	Treatment of Hepatitis C Coinfection
	• Antiviral treatment for HCV infection should be considered for all HIV-infected persons with acute or chronic HCV infection. In the absence of contraindications to peginterferon and/or ribavirin, treatment for HCV infection should be routinely offered to persons in whom the potential benefits of therapy are judged to outweigh the potential risks, including (but not limited to) persons with:
	  ○ HCV genotype 2 or 3 infection
	  ○ HCV genotype 1 infection with a low HCV RNA level (<800,000 IU/mL)
	  ○ Significant hepatic fibrosis (bridging fibrosis or cirrhosis)

Clinical Guideline	Recommendation(s)
	○ Stable HIV infection not requiring ART ○ Acute HCV infection (<6 months duration) ○ Cryoglobulinemic vasculitis ○ Cryoglobulinemic membranoproliferative glomerulonephritis ○ Strong motivation to treat their HCV infection • On the basis of well-designed, randomized, controlled trials, peginterferon plus ribavirin is the recommended treatment for hepatitis C in HIV-infected persons. • For all HCV genotypes, the recommended treatment regimen includes peginterferon alfa-2a or peginterferon alfa-2b plus oral ribavirin for a total duration of 48 weeks. • Patients with contraindications to the use of ribavirin can be treated with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower SVR rates are expected in persons not receiving ribavirin.
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**[15] **(2009)**	Cytomegalovirus (CMV) Recommendations • Hematopoietic cell transplantation (HCT) candidates should be tested for CMV antibodies prior to transplant to determine their risk for primary CMV infection and reactivation after HCT. • CMV-seropositive HCT recipients and CMV-seronegative recipients with CMV-seropositive donors should be placed on CMV preventative therapy from time of engraftment until at least 100 days after HCT. • A prophylaxis strategy against early CMV replication for allogeneic recipients involves administering prophylaxis to all allogeneic recipients at risk throughout the period from engraftment to 100 days after HCT. Ganciclovir, high-dose acyclovir and valacyclovir are all effective at reducing the risk for CMV infection after HCT. • Ganciclovir is often used as a first-line drug for preemptive therapy. Although foscarnet is as effective as ganciclovir, it is currently more commonly used as a second-line drug, because of the requirement for pre-hydration and electrolyte monitoring. Preemptive therapy should be given for a minimum of 2 weeks. Patients who are ganciclovir-intolerant should be treated with foscarnet. Herpes Simplex Virus (HSV) Recommendations • Acyclovir prophylaxis should be offered to all HSV-seropositive allogenic recipients to prevent HSV reactivation during the early transplant period for up to 30 days. • Routine acyclovir prophylaxis is not indicated for HSV-seronegative allogenic recipients. • Use of ganciclovir for CMV prophylaxis will provide sufficient prophylaxis for HSV. • Foscarnet is the treatment of choice for acyclovir-resistant HSV. • Valacyclovir is equally effective at HSV prophylaxis when compared to acyclovir. • Foscarnet is not recommended for routine HSV prophylaxis among HCT recipients due to renal and infusion-related toxicity. Patients who receive foscarnet for other reasons (e.g., CMV prophylaxis) do not require additional acyclovir prophylaxis. • There is inadequate data to make recommendations regarding the use of famciclovir for HSV prophylaxis. • HSV prophylaxis lasting >30 days after HCT might be considered for persons with frequent recurrences of HSV infection. Acyclovir or valacyclovir can be used during phase I (pre-engraftment) for administration to HSV-seropositive autologous recipients who are likely to experience substantial mucositis from the conditioning regimen.

Clinical Guideline	Recommendation(s)
	Varicella Zoster Virus (VZV) Recommendations • Long-term acyclovir prophylaxis to prevent recurrent VZV infection is recommended for the first year after HCT for VZV-seropositive allogenic and autologous HCT recipients. Acyclovir prophylaxis may be continued beyond 1 year in allogenic HCT recipients who have GVDH or require systemic immunosuppression. • Valacyclovir may be used in place of acyclovir when oral medications are tolerated. • There is not enough data to recommend use of famciclovir in place of valacyclovir or acyclovir for VZV prophylaxis. • Any HCT recipient with VZV-like rash should receive preemptive IV acyclovir therapy until 2 days after the lesions have crusted • Acyclovir or valacyclovir may be used in place of VZV immunoglobulin for post-exposure therapy. Hepatitis B Virus (HBV) Recommendations • Limited data suggests HCT donors with detectable HBV DNA should receive antiviral therapy for 4 weeks or until viral load is undetectable. Expert opinion suggests entecavir for this use. • HCT recipients with active HBV posttransplant should be treated with lamivudine for at least 6 months in autologous HCT recipients and for 6 months after immunosuppressive therapy has stopped in allogenic HCT recipients. Hepatitis C Virus (HCV) Recommendations • Treatment for chronic HCV should be considered in all HCV-infected HCT recipients. • The patient must be in complete remission from the original disease, be >2 years posttransplant without evidence of either protracted GVHD, have been off immunosuppression for 6 months, and have normal blood counts and serum creatinine. • Treatment should consist of full-dose peginterferon and ribavirin and should be continued for 24 to 48 weeks, depending on response.
Infectious Diseases Society of America (IDSA): **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer**[102] **(2010)**	Antiviral Prophylaxis • Herpes simplex virus (HSV)–seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive acyclovir antiviral prophylaxis. • Antiviral treatment for HSV or varicella-zoster virus (VZV) infection is only indicated if there is clinical or laboratory evidence of active viral disease.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the nucleosides and nucleotides are noted in Tables 3-4. 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 3. FDA-Approved Indications for the Nucleosides and Nucleotides (Drugs A-F)[1-14]

Indication	Acyclovir	Adefovir	Cidofovir	Entecavir	Famciclovir
Cytomegalovirus Infection					
Treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome (AIDS)			✔		
Hepatitis B Virus Infection					
Treatment of chronic hepatitis B in patients with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease		✔		✔	
Herpes Simplex Virus Infection					
Treatment of herpes genitalis	✔				✔
Treatment of herpes labialis					✔
Treatment of herpes simplex encephalitis	✔ §				
Treatment of mucocutaneous herpes simplex virus infections in immunocompromised patients	✔ §				
Treatment of neonatal herpes simplex virus infections	✔ §				
Treatment of recurrent orolabial or genital herpes in HIV-infected adults					✔
Varicella-Zoster Virus Infection					
Treatment of chickenpox	✔ ‡				
Treatment of herpes zoster (shingles)	✔ ‡				✔
Treatment of herpes zoster (shingles) infection in immunocompromised patients	✔ §				

§Intravenous formulation only
‡Oral formulations only

Table 4. FDA-Approved Indications for the Nucleosides and Nucleotides (Drugs G-V)[1-14]

Indication	Ganciclovir	Ribavirin	Telbivudine	Valacyclovir	Valganciclovir
Cytomegalovirus Infection					
Prevention of cytomegalovirus disease in transplant recipients at risk from CMV disease	✔				
Prevention of cytomegalovirus disease in pediatric kidney or heart transplant patients at high risk					✔
Prevention of cytomegalovirus disease in adult kidney, heart, or kidney-pancreas transplant patients at high risk					✔
Treatment of cytomegalovirus retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS)	✔				
Treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome (AIDS)					✔
Hepatitis B Virus Infection					
Treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease			✔		
Hepatitis C Virus Infection					
Treatment of chronic hepatitis C in combination with interferon alfa-2b (pegylated and non-pegylated) in patients with compensated liver disease		✔ ‡			
Treatment of chronic hepatitis C in combination with peginterferon alfa-2a in patients with compensated liver disease and who have not been previously treated with interferon alpha		✔ §			
Herpes Simplex Virus Infection					
Chronic suppressive therapy of recurrent episodes of genital herpes in immunocompetent and in HIV-1-infected adults				✔	
Reduction of transmission of genital herpes in immunocompetent adults				✔	
Treatment of the initial episode of genital herpes in immunocompetent adults				✔	
Treatment of recurrent episodes of genital herpes in immunocompetent adults				✔	
Treatment of herpes labialis				✔	
Respiratory Syncytial Virus					
Treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus		✔ †			
Varicella-Zoster Virus Infection					
Treatment of chickenpox				✔	
Treatment of herpes zoster (shingles) in immunocompetent adults				✔	

‡Capsule formulation only
†Inhalation formulation only
§Tablet formulation only

IV. Pharmacokinetics

The pharmacokinetic parameters of the nucleosides and nucleotides are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Nucleosides and Nucleotides[1-14]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Acyclovir	Oral: 10-20	9-33	Not reported	Renal (62-91)	2.2-20
Adefovir	59	≤4	Intestinal, Liver	Renal (45)	7.5
Cidofovir	Not reported	≤6	Not reported	Renal (80-100)	2.5
Entecavir	100	13	Not reported	Renal (62-73)	24
Famciclovir	75-77	<20	Liver	Renal (73)	2-2.3
Ganciclovir	5	1-2	Not reported	Renal (91)	3.5
Ribavirin	Oral: 20-64	0	Not reported	Renal (40-60)	Inh: 9.5 Oral: 298
Telbivudine	Not reported	3.3	Not reported	Renal (42)	40-49
Valacyclovir	55	14-18	Liver	Renal (42)	2.5-3.3
Valganciclovir	60	Not reported	Not reported	Renal	4

V. Drug Interactions

Significant drug interactions with the nucleosides and nucleotides are listed in Table 6.

Table 6. Significant Drug Interactions with the Nucleosides and Nucleotides[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Ganciclovir, valganciclovir	1	Zidovudine	Coadministration of ganciclovir with zidovudine may result in life-threatening hematologic toxicity.
Ribavirin	1	Nucleoside analogues	Administration of nucleoside analogues has resulted in fatal and nonfatal lactic acidosis.
Ribavirin	1	Thiopurines	Inhibition of inosine monophosphate dehydrogenase (IMPDH) by ribavirin may increase the concentration of methylated metabolites of thiopurines leading to myelotoxicity.
Ganciclovir, valganciclovir	2	Didanosine	Plasma concentrations and pharmacologic effects of didanosine may be increased by ganciclovir. Didanosine toxicity may result.
Ganciclovir, valganciclovir	2	Probenecid	Plasma concentrations of ganciclovir may be increased by probenecid. Ganciclovir toxicity may result.
Telbivudine	2	Interferons	Coadministration of telbivudine with interferons may increase telbivudine induced peripheral neuropathy.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the nucleosides and nucleotides are listed in Table 7. The boxed warnings for the nucleosides and nucleotides are listed in Tables 8-15.

Table 7. Adverse Drug Events (%) Reported with the Nucleosides and Nucleotides[1-14]

Adverse Events	Acyclovir	Adefovir	Cidofovir	Entecavir	Famciclovir	Ganciclovir	Ribavirin	Telbivudine	Val-acyclovir	Val-ganciclovir
Cardiovascular System										
Cardiac arrest	-	-	-	-	-	✔	-	-	-	-
Chest pain	-	-	-	-	-	-	5-9	-	-	-
Conduction abnormalities	-	-	-	-	-	✔	✔	-	-	-
Flushing	-	-	-	-	-	-	4	-	-	-
Hypertension	-	-	-	-	-	✔	-	-	✔	12-18
Hypotension	✔	-	✔	-	-	✔	-	-	-	-
Tachycardia	-	-	-	-	-	-	-	-	✔	✔
Torsades de Pointes	-	-	-	-	-	✔	-	-	-	-
Ventricular tachycardia	-	-	-	-	-	✔	-	-	-	-
Central Nervous System										
Abnormal dreams	-	-	-	-	-	✔	-	-	-	-
Abnormal thinking	-	-	-	-	-	✔	-	-	-	-
Agitation	✔	-	✔	-	-	-	10-33	-	✔	✔
Anxiety	-	-	✔	-	-	✔	✔	-	-	-
Ataxia	✔	-	✔	-	-	-	-	-	✔	-
Chills	-	-	22	-	-	10	-	-	-	-
Coma	✔	-	-	-	-	-	✔	-	✔	-
Confusion	✔	-	✔	-	✔	✔	10-21	-	✔	✔
Depression	✔	-	✔	-	-	✔	13-36	-	-	✔
Dizziness	✔	-	✔	<1	✔	✔	17-26	4	3	✔
Extrapyramidal symptoms	-	-	-	-	-	✔	-	-	-	-
Fatigue/lethargy/malaise	12	-	-	1	1-5	✔	14-70	13	-	✔
Fever	✔	-	14-58	-	-	48	32-61	4	-	31
Hallucinations	✔	-	✔	-	✔	✔	✔	-	-	✔
Headache	2	9	30	2	9-39	✔	43-69	10	13-38	6-22
Insomnia	✔	-	✔	<1	-	✔	26-41	3	-	6-20
Malaise	-	-	-	-	-	-	6	-	-	-
Memory impairment	-	-	-	-	-	-	6	-	-	-
Neuropathy	-	-	-	-	-	9	✔	-	-	9
Paresthesia	✔	-	✔	-	1-3	✔	-	-	-	8

Adverse Events	Acyclovir	Adefovir	Cidofovir	Entecavir	Famciclovir	Ganciclovir	Ribavirin	Telbivudine	Val-acyclovir	Val-ganciclovir
Psychotic reactions	✔	-	-	-	-	-	✔	-	✔	✔
Seizure	✔	-	✔	-	-	✔	-	-	✔	✔
Somnolence/drowsiness	✔	-	-	<1	✔	✔	-	-	-	-
Suicidal ideation	-	-	-	-	-	-	1-2	-	-	-
Tremors	-	-	22	-	-	✔	25-48	-	✔	12-28
Dermatological										
Alopecia	-	-	27	✔	-	✔	27-36	-	✔	-
Dry skin	-	-	-	-	-	-	10-25	-	-	-
Eczema	-	-	-	-	-	-	4-5	-	-	-
Erythema multiforme	-	-	-	-	✔	-	-	-	✔	-
Photosensitivity	-	-	-	-	-	-	12-21	-	✔	-
Pruritus	2	✔	✔	-	<4	5	13-29	2	✔	✔
Rash	2	✔	30	✔	<3	✔	17-28	4	✔	-
Stevens-Johnson syndrome	✔	-	-	-	✔	✔	✔	-	-	-
Toxic epidermal necrolysis	✔	-	-	-	✔	-	-	-	-	-
Urticaria	2	-	-	-	✔	-	-	-	✔	-
Gastrointestinal										
Abdominal pain/discomfort	✔	9	✔	-	<8	✔	8	6	1-11	15
Anorexia	✔	-	23	-	-	14	21-51	-	-	✔
Aphthous stomatitis	-	-	-	-	-	✔	-	-	-	-
Constipation	-	-	-	-	-	✔	5	-	-	-
Dehydration	-	-	-	-	-	-	-	-	2	✔
Diarrhea	2-3	3	26	<1	2-9	44	11	6	1-5	16-41
Dyspepsia/heartburn	-	3	-	<1	-	✔	<1-16	3	-	✔
Dysphagia	-	-	-	-	-	✔	-	-	-	-
Eructation	-	-	-	-	-	✔	-	-	-	-
Flatulence	-	4	-	-	<5	✔	-	-	-	-
Nausea	2-7	5	7-69	<1	2-13	-	25-47	5	5-15	8-30
Oral moniliasis	-	-	18	-	-	-	-	-	-	-
Taste perversion	-	-	-	-	-	-	4-9	-	-	-
Ulceration	-	-	-	-	-	✔	✔	-	-	-
Vomiting	3-7	✔	7-69	<1	1-5	13	9-42	-	6	3-21
Weight loss	-	-	-	-	-	-	10-29	-	-	-
Xerostomia	-	-	-	-	-	-	12	-	-	-
Genitourinary										
Glycosuria	-	-	-	4	-	-	-	-	-	-
Hematuria	✔	11	-	9	-	-	-	-	-	-

Adverse Events	Acyclovir	Adefovir	Cidofovir	Entecavir	Famciclovir	Ganciclovir	Ribavirin	Telbivudine	Val-acyclovir	Val-ganciclovir
Proteinuria/albuminuria	-	-	50	-	-	-	-	-	-	-
Hematological										
Anemia	✔	-	24	-	<1	5-26	11-17	-	-	7-16
Aplastic anemia	-	-	-	-	-	-	✔	-	✔	✔
Hematocrit decreased	-	-	-	-	-	5-26	11-35	-	<1	-
Hemoglobin decreased	-	-	-	-	-	5-26	11-35	-	<1	-
Hemolytic anemia	-	-	-	-	-	-	10-13	-	-	-
Leukocytosis	✔	-	-	-	-	-	-	-	-	-
Leukopenia	✔	-	-	-	1	41	6-45	-	-	-
Monocytes increased	-	-	-	-	-	-	-	-	-	-
Neutropenia	-	-	24-43	-	3	14-26	8-42	2	≤18	17-19
Thrombocytopenia	✔	-	-	-	✔	6	1-15	<1	3	6-22
Laboratory Test Abnormalities										
Alkaline phosphatase	-	-	-	-	-	-	-	-	4	-
ALT/AST increased	1-2	8-20	-	2-12	2-3	✔	1-3	3-7	2-16	-
Bilirubin increased/decreased	✔	-	-	2-3	2	-	10-32	<1	-	-
BUN increased	5-10	-	-	-	-	-	-	-	-	-
Creatine phosphokinase increased	-	-	-	-	-	-	-	11-13	-	-
Hyperglycemia	-	-	-	2-3	-	-	-	-	-	✔
Hyperkalemia	-	-	-	-	-	-	-	-	-	✔
Hyperuricemia	-	-	-	-	-	-	33-38	-	-	-
Hypokalemia	-	-	-	-	-	-	-	-	-	✔
Hyponatremia	-	-	-	-	-	✔	-	-	-	-
Hypophosphatemia	-	-	-	-	-	-	-	-	-	✔
Lactic acidosis	-	-	-	✔	-	-	-	✔	-	-
Serum bicarbonate decreased	-	-	16	-	-	-	-	-	-	-
Serum creatinine increased	5-10	32-51	12	1-2	<1	2-50	-	-	-	3-50
Musculoskeletal										
Arthralgia/myalgia	✔	-	-	-	-	-	-	3-4	1-6	✔
Asthenia	-	13	43	-	-	-	5-10	-	-	-
Rhabdomyolysis	-	-	-	-	-	✔	-	✔	-	-
Respiratory										
Cough	-	6-8	19	-	-	✔	7-23	6	-	-
Dyspnea	-	-	8-23	-	-	✔	5-26	-	✔	✔
Nasopharyngitis	-	-	-	-	-	-	13	-	16	✔

Adverse Events	Acyclovir	Adefovir	Cidofovir	Entecavir	Famciclovir	Ganciclovir	Ribavirin	Telbivudine	Val-acyclovir	Val-ganciclovir
Respiratory tract infection	-	-	9	-	-	-	-	-	9	-
Rhinitis/ rhinorrhea	-	5	-	-	-	-	8	-	2	✔
Special Senses										
Decreased intraocular pressure	-	-	24	-	-	-	-	-	-	-
Iritis	-	-	✔	-	-	-	-	-	-	-
Retinal detachment	-	-	-	-	-	-	-	-	-	15
Tinnitus	-	-	-	-	-	✔	19-28	-	-	-
Uveitis	-	-	✔	-	-	-	-	-	-	-
Visual disturbances	✔	-	✔	-	-	✔	5	-	✔	-
Other										
Anaphylaxis	-	-	-	✔	-	✔	✔	-	✔	✔
Dysmenorrhea	-	-	-	-	<8	-	-	-	1-8	-
Edema	✔	-	-	-	-	-	-	-	-	✔
Fanconi syndrome	-	✔	1	-	-	-	-	-	-	-
Flu-like symptoms	-	-	-	-	-	-	13-31	-	-	-
Infection	-	-	12-28	-	-	13	3-6	-	-	✔
Injection site reactions	9	-	✔	-	-	✔	5-23	-	-	-
Pain	✔	-	25	-	-	✔	5	4	-	✔
Sepsis	-	-	-	-	-	15	-	-	-	✔
Sweating	-	-	-	-	-	12	11	-	-	-
Weakness	-	-	-	-	-	-	9-10	-	-	-

✔ Percent not specified
- Event not reported

Table 8. Boxed Warning for Adefovir[1]

WARNING
Severe acute exacerbations of hepatitis have been reported in patients who have discontinued anti–hepatitis B therapy, including adefovir. Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who discontinue anti–hepatitis B therapy. If appropriate, resumption of anti–hepatitis B therapy may be warranted. In patients at risk of or having underlying renal dysfunction, chronic administration of adefovir may result in nephrotoxicity. Closely monitor renal function in these patients; they may require dose adjustment. HIV resistance may emerge in chronic hepatitis B patients with unrecognized or untreated HIV infection treated with anti–hepatitis B therapies that may have activity against HIV (e.g., adefovir). Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals.

Table 9. Boxed Warning for Cidofovir[1]

WARNING
Renal impairment is the major toxicity of cidofovir. Cases of acute renal failure resulting in dialysis or contributing to death have occurred with as few as 1 or 2 doses of cidofovir. To reduce possible nephrotoxicity, IV prehydration with normal saline and administration of probenecid must be used with each cidofovir infusion. Renal function (serum creatinine and urine protein) must be monitored within 48 hours prior to each dose of cidofovir and the dose of cidofovir modified for changes in renal function as appropriate (see Administration and Dosage). Cidofovir is contraindicated in patients who are receiving other nephrotoxic agents. Neutropenia has been observed in association with cidofovir treatment. Therefore, neutrophil counts should be monitored during cidofovir therapy. Cidofovir is indicated only for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS). In animal studies, cidofovir was carcinogenic, teratogenic and caused hypospermia (see Warnings, Carcinogenesis, Mutagenesis, and Fertility impairment).

Table 10. Boxed Warning for Entecavir[1]

WARNING
Severe acute exacerbations of hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued antihepatitis B therapy, including entecavir. Closely monitor hepatic function with clinical and laboratory follow-up for at least several months in patients who discontinue antihepatitis B therapy. If appropriate, initiation of antihepatitis B therapy may be warranted. **Patients co-infected with HIV and chronic hepatitis B virus:** Limited clinical experience suggests there is a potential for the development of resistance to HIV nucleoside reverse transcriptase inhibitors (NRTIs) if entecavir is used to treat chronic hepatitis B virus (HBV) infection in patients with HIV infection that is not being treated. Therapy with entecavir is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART). **Lactic acidosis and severe hepatomegaly:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with antiretrovirals.

Table 11. Boxed Warning for Ganciclovir[1]

WARNING
The clinical toxicity of ganciclovir IV includes granulocytopenia, anemia and thrombocytopenia. In animal studies ganciclovir was carcinogenic, teratogenic and caused aspermatogenesis. Ganciclovir IV is indicated for use only in the treatment of cytomegalovirus (CMV) retinitis in immunocompromised patients and for the prevention of CMV disease in transplant patients at risk for CMV disease.

Table 12. Boxed Warning for Ribavirin (Inhalation Solution)[1]

WARNING
Use of aerosolized ribavirin in patients requiring mechanical ventilator assistance should be undertaken only by health care providers and support staff familiar with this mode of administration and the specific ventilator being used. Strict attention must be paid to procedures that have been shown to minimize the accumulation of drug precipitate, which can result in mechanical ventilator dysfunction and associated increases in pulmonary pressures. Sudden deterioration of respiratory function has been associated with the initiation of aerosolized ribavirin use in infants. Carefully monitor respiratory function during treatment. If the initiation of aerosolized ribavirin treatment appears to produce sudden deterioration of respiratory function, stop treatment and reinstitute it only with extreme caution, continuous monitoring, and consideration of coadministration of bronchodilators. Aerosolized ribavirin is not indicated for use in adults. Be aware that ribavirin has been shown to produce testicular lesions in rodents and to be teratogenic in all animal species in which adequate studies have been conducted (rodents and rabbits).

Table 13. Boxed Warning for Ribavirin (Oral)[1]

WARNING
Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus (HCV) infection and should not be used alone for this indication. The primary clinical toxicity of ribavirin is hemolytic anemia, which may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions (MIs). Do not treat patients with a history of significant or unstable cardiac disease with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days, and it may persist in nonplasma compartments for as long as 6 months. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and female partners of male patients who are taking ribavirin therapy. At least 2 reliable forms of effective contraception must be used during treatment and during the 6-month posttreatment follow-up period.

Table 14. Boxed Warning for Telbivudine[1]

WARNING
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with antiretrovirals. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti–hepatitis B therapy, including telbivudine. Closely monitor hepatic function with clinical and laboratory follow-up for at least several months in patients who discontinue anti–hepatitis B therapy. If appropriate, resumption of anti–hepatitis B therapy may be warranted.

Table 15. Boxed Warning for Valganciclovir[1]

WARNING
The clinical toxicity of valganciclovir, which is metabolized to ganciclovir, includes granulocytopenia, anemia, and thrombocytopenia. In animal studies, ganciclovir was carcinogenic and teratogenic and caused aspermatogenesis.

VII. Dosing and Administration

The usual dosing regimens for the nucleosides and nucleotides are listed in Table 16.

Table 16. Usual Dosing Regimens for the Nucleosides and Nucleotides[1-14]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Acyclovir	Chickenpox: Oral : 800 mg every 4 hours, 5 times daily for 5 days Herpes Genitalis: Initial therapy: IV: 5 mg/kg infused over 1 hour, every 8 hours for 5 days Oral: 200 mg every 4 hours, 5 times daily for 10 days Chronic suppressive therapy: Oral: 400 mg twice daily for up to 12 months; alternative regimens include 200 mg 3 times daily to 200 mg 5 times daily Intermittent therapy: Oral: 200 mg every 4 hours, 5 times daily for 5 days Herpes Simplex Encephalitis: IV: 10 mg/kg infused over 1 hour, every 8 hours for 10 days Herpes Simplex Infections In Immunocompromised Patients (Mucocutaneous): IV: 5 mg/kg infused over 1 hour, every 8 hours for 7 days Herpes Zoster: Oral : 800 mg every 4 hours, 5 times daily for 7-10 days Varicella Zoster Infections In Immunocompromised Patients: IV: 10 mg/kg infused over 1 hour, every 8 hours for 7 days	Chickenpox: ≥2 years of age: Oral: 20 mg/kg per dose 4 times daily >40 kg: Oral : 800 mg every 4 hours, 5 times daily for 5 days Herpes Simplex Encephalitis: Birth to 3 months of age: IV: 10 mg/kg infused over 1 hour, every 8 hours for 10 days 3 months to ≤12 years of age: IV: 20 mg/kg infused over 1 hour, every 8 hours for 10 days ≥12 years of age: IV: 10 mg/kg infused over 1 hour, every 8 hours for 10 days Herpes Simplex Infections In Immunocompromised Patients (Mucocutaneous): <12 years of age: IV: 10 mg/kg infused over 1 hour, every 8 hours for 7 days. Children ≥12 years of age should receive adult dose. Varicella Zoster Infections In Immunocompromised Patients: <12 years of age: IV: 20 mg/kg infused over 1 hour, every 8 hours for 7 days. ≥12 years of age: IV: 10 mg/kg infused over 1 hour, every 8 hours for 7 days	Capsule: 200 mg Injection: 50 mg/ml 500 mg 1,000 mg Suspension: 200 mg/5 ml Tablet: 400 mg 800 mg
Adefovir	Chronic Hepatitis B: 10 mg once daily	Chronic Hepatitis B: ≥12 years of age: 10 mg once	Tablet: 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		daily	
Cidofovir	Cytomegalovirus Retinitis: Induction: 5 mg/kg once weekly for 2 weeks Maintenance: 5 mg/kg once every 2 weeks	Safety and efficacy in children have not been established.	Injection: 75 mg/ml
Entecavir	Chronic Hepatitis B (Compensated Liver Disease): Nucleoside-treatment-naïve patients: 0.5 mg once daily Lamivudine or telbivudine resistance: 1 mg once daily Chronic Hepatitis B (Decompensated Liver Disease): 1 mg once daily	Chronic Hepatitis B (Compensated Liver Disease): ≥16 years of age: Nucleoside-treatment-naïve patients: 0.5 mg once daily Lamivudine or telbivudine resistance: 1 mg once daily	Solution: 0.05 mg/ml Tablet: 0.5 mg 1 mg
Famciclovir	Herpes Genitalis: Immunocompetent patients: Recurrent episodes: 1,000 mg twice daily for 1 day Suppressive therapy: 250 mg twice daily HIV-infected patients: Recurrent episodes: 500 mg twice daily for 7 days Herpes Labialis: Immunocompetent patients: 1,500 mg as a single dose HIV-infected patients: 500 mg twice daily for 7 days Herpes Zoster (Shingles): Immunocompetent patients: 500 mg every 8 hours for 7 days	Safety and efficacy in children have not been established.	Tablet: 125 mg 250 mg 500 mg
Ganciclovir	Cytomegalovirus Retinitis: Induction: 5 mg/kg IV every 12 hours for 14 to 21 days Maintenance: 5 mg/kg IV once daily, 7 days per week, or 6 mg/kg IV once daily, 5 days per week Prophylaxis of Cytomegalovirus Disease in Transplant Patients: 5 mg/kg IV every 12 hours for 7 to 14 days, followed by 5 mg/kg IV once daily, 7 days per week or 6 mg/kg IV once daily, 5 days	Safety and efficacy in children have not been established.	Injection: 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	per week		
Ribavirin	Chronic Hepatitis C: Capsule/solution (combination with interferon alfa-2b): Interferon alfa-naïve patients: ≤75 kg: 1,000 mg/day >75 kg: 1,200 mg/day The recommended duration of treatment is 24 to 48 weeks, which should be individualized depending on baseline disease characteristics, response to therapy, and tolerability of the regimen. Retreatment in patients who relapse following non-pegylated interferon monotherapy: ≤75 kg: 1,000 mg/day >75 kg: 1,200 mg/day The recommended duration of treatment is 24 weeks. Chronic Hepatitis C: Capsule/solution (combination with peginterferon alfa-2b): Interferon alfa-naïve patients: 800 to 1,400 mg/day (based on body weight) for 24 weeks (genotypes 2/3) or 48 weeks (genotype 1) Retreatment of prior treatment failures: 800 to 1,400 mg/day (based on body weight) for 48 weeks, regardless of HCV genotype Chronic Hepatitis C Monoinfection (Genotypes 1/4): Tablet (combination with peginterferon alfa-2a): <75 kg: 1,000 mg daily for 48 weeks ≥75 kg: 1,200 mg daily for 48 weeks Chronic Hepatitis C Monoinfection (Genotypes 2/3): Tablet (combination with peginterferon alfa-2a): 800 mg daily for 24 weeks	Chronic Hepatitis C: ≥3 years of age: Capsule/solution (combination with interferon alfa-2b or peginterferon alfa-2b): <47 kg: 15 mg/kg/day 47-59 kg: 800 mg/day 60-73 kg: 1,000 mg/day >73 kg: 1,200 mg/day Treatment duration is 24 weeks for genotypes 2/3 and 48 weeks for genotype 1. Chronic Hepatitis C Monoinfection: ≥5 years of age: Tablet (combination with peginterferon alfa-2a): 22-33 kg: 400 mg/day 34-46 kg: 600 mg/day 47-59 kg: 800 mg/day 60-74 kg: 1,000 mg/day ≥75 kg: 1,200 mg/day Respiratory Syncytial Virus: Inhalation: 20 mg/ml for 12 to18 hours per day for 3 to 7 days	Capsule: 200 mg Tablet dose pack: 400-400 mg 600-400 mg 600-600 mg Inhalation solution: 6 g Solution: 40 mg/ml Tablet: 200 mg 400 mg 600 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Chronic Hepatitis C With HIV Coinfection: Tablet (combination with peginterferon alfa-2a): 800 mg daily for 48 weeks regardless of HCV genotype		
Telbivudine	Chronic Hepatitis B: 600 mg once daily	Chronic Hepatitis B: ≥16 years of age: 600 mg once daily	Tablet: 600 mg
Valacyclovir	Herpes Genitalis: Initial episode: 1 g twice daily for 10 days Recurrent episodes: 500 mg twice daily for 3 days Reduction of transmission: 500 mg once daily for the source partner Suppressive therapy: 1 g once daily Herpes Labialis: 2 g twice daily for 1 day Herpes Zoster: 1 g every 3 times daily for 7 days	Chickenpox: 2-18 years of age: 20 mg/kg 3 times daily for 5 days Herpes Labialis: ≥12 years of age: 2 g twice daily for 1 day	Tablet: 500 mg 1,000 mg
Valganciclovir	Cytomegalovirus Retinitis: Induction: 900 mg twice daily for 21 days Maintenance: 900 mg once daily Prevention of Cytomegalovirus Disease: Heart or kidney-pancreas transplant: 900 mg once daily starting within 10 days of transplantation until 100 days posttransplantation Kidney transplant: 900 mg once daily starting within 10 days of transplantation until 200 days posttransplantation	Prevention of Cytomegalovirus Disease: 4 months to 16 years of age: Kidney or heart transplant: The dose is calculated based on body surface area and creatinine clearance, which is administered once daily starting within 10 days of transplantation until 100 days posttransplantation	Solution: 50 mg/ml Tablet: 450 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the nucleosides and nucleotides are summarized in Table 17.

Table 17. Comparative Clinical Trials with the Nucleosides and Nucleotides

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cytomegalovirus Infections				
Thomas et al.[93] (2009) Acyclovir 800 mg TID for 6 months All patients received triple immuno-suppressive therapy.	RETRO Patients who received a lung or heart transplant who were CMV seropositive or had CMV seropositive donors	N=78 Mean 4.3 years	Primary: Risk of CMV disease and infection at 1 year, graft dysfunction	Primary: The one-year risk of CMV infection was similar in R-/D+ and R+/D+ patients (76% and 75%, respectively). R+/D- patients had significantly lower risk of CMV infection compared to all D+ patients (40%, P=0.002). R-/D+ patients had a one-year risk of CMV disease of 37% compared with a 2% risk in R+ patients (P<0.0001). CMV disease developed after a mean of 90 days after transplantation. Acute rejection episodes were similar between all groups (R-/D+ 65%, R+/D+ 66%, R+/D- 65%, P=0.1). Acute rejection was not more common in patients with CMV infection (66%) versus those without CMV infection (64%; P=0.1). Acute rejection was not more common in patients with CMV disease (71%) versus those without CMV infection (65%; P=0.1). Patients with CMV infection had a higher cumulative risk of graft dysfunction at 1 year (P=0.012).
Flechner et al.[39] (1998) Acyclovir 800 mg QD, 800 mg BID, 800 mg TID, or 800 QID vs	PRO, RCT Adult recipients of their first or second kidney-only transplants	N=101 Mean 14 months	Primary: Time to CMV infection during the first 6 months after trans-plantation Secondary: Incidence symptomatic CMV	Primary: At the 6-month observation point, CMV was isolated in 14 of 39 (35.9%) acyclovir-treated patients compared to 1 of 40 (2.5%) ganciclovir-treated patients (P=0.0001). Secondary: Symptomatic CMV disease occurred in 9 of the 14 infected acyclovir-treated patients compared to none in the ganciclovir-treated group (P=0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ganciclovir 500 mg, 1,000 mg QD, 1,000 mg BID or 1,000 mg TID			disease	Drug-related adverse events were not reported.
Burns et al.[40] (2002) Acyclovir 800 mg PO 5 times a day to day 100 after transplantation vs ganciclovir 5 mg/kg IV every weekday (Monday-Friday) to day 100 All patients received IV ganciclovir 5 mg/kg every 12 hours 7 days to 2 days prior to transplantation, then acyclovir IV 10 mg/kg every 8 hours from 1 day prior until neutrophil engraftment.	RCT Patients undergoing allogenic stem cell transplant positive for CMV antibodies	N=91 100 days	Primary: Incidence of CMV antigenemia (≥1 positive cell/ 50,000 leukocytes examined) Secondary: Incidence of CMV disease at 1 year and survival rates	Primary: CMV antigenemia occurred in 41% of patients taking acyclovir compared to 31% of those taking ganciclovir (P=0.22). Secondary: CMV disease occurred in 17% of patients taking acyclovir compared to 13% of those taking ganciclovir (P=0.59). Survival of patients 1 year after transplant was similar between treatment groups (64% on ganciclovir vs 54% on acyclovir, P=0.38). There were 3 deaths associated with CMV disease in the acyclovir-treated group and 1 death in the ganciclovir-treated group (P=0.38). Drug-related adverse events were not reported.
Rubin et al.[41] (2000) Acyclovir 400 mg	RCT Patients ≥12 years old undergoing a	N=155 12 weeks	Primary: Incidence of CMV disease in 6 months post-	Primary: Significantly more CMV disease occurred in patients taking acyclovir compared to those receiving ganciclovir (32% vs 50%, P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
PO TID vs ganciclovir 1,000 mg PO TID All patients received IV ganciclovir 5 mg/kg/day for 5 to 10 days after transplantation.	first kidney, heart or liver transplant and positive for CMV antibodies		transplant Secondary: Occurrence of allograft rejections, clinical infection rates, lympho-proliferative disease, and drug toxicities	Secondary: Allograft rejections occurred in 46% of patients taking acyclovir compared to 46% of those receiving ganciclovir (P=NS). There were no differences in the overall incidence of non-CMV infection between the two treatment groups. Leukopenia developed in 12 patients treated with ganciclovir and 2 patients treated with acyclovir (P<0.05). Thrombocytopenia rates were comparable in both treatment groups. No patients had to discontinue their CMV prophylaxis due to these episodes.
Winston et al.[42] (2003) Acyclovir 800 mg PO every 6 hours from day 15 to day 100 after transplantation vs ganciclovir 1,000 mg PO every 8 hours from day 15 to day 100 All patients received IV ganciclovir 6 mg/kg/day from day 1 to day 14 after transplantation.	RCT Patients undergoing liver transplant positive for CMV antibodies	N=219 100 days	Primary: Incidence of CMV disease, rates of leukopenia and thrombocytopenia, survival after 1 year	Primary: CMV disease occurred in 7.3% of patients taking acyclovir compared to 0.9% of those receiving ganciclovir (P=0.019). Leukopenia occurred in 35% of patients treated with ganciclovir and 18% of patients being treated with acyclovir (P=0.009). Sixteen patients (15%) on ganciclovir had to discontinue their CMV prophylaxis due to leukopenia compared to none on acyclovir (P<0.001). Total and severe rates of thrombocytopenia were comparable in both treatment groups. Survival of patients 1 year after transplant was similar between treatment groups (81% on ganciclovir vs 85% on acyclovir). Only one death associated with CMV disease occurred, and that death occurred in an acyclovir-treated patient. The incidence of drug-related adverse events was not reported.
Winston et al.[43]	RCT	N=250	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(1995) Acyclovir 800 mg PO QID to day 100 after transplantation vs ganciclovir 5 mg/kg IV every weekday (Monday-Friday) to day 100 after transplantation All patients received IV ganciclovir 6 mg/kg/day from postoperative day 1 to day 30.	Patients undergoing liver transplant	100 days	Incidence of CMV infection Secondary: Incidence of CMV disease	Significantly more CMV infection occurred in patients taking acyclovir compared to those receiving ganciclovir (38% vs 5%, P<0.0001). Secondary: Symptomatic CMV disease occurred at a significantly higher incidence in those patients taking acyclovir compared to those receiving ganciclovir (10% vs 0.8%, P=0.002). Drug-related adverse events reported were comparable between the two treatment groups.
Ljungman et al.[44] (2002) Acyclovir 800 mg QID until week 18 after transplantation vs valacyclovir PO 2,000 mg QID until week 18 after transplantation	DB, MC, RCT Patients age ≥13 years old that received an allogenic bone marrow transplant (BMT) seropositive for CMV antibody	N=748 18 weeks	Primary: Time to CMV infection in blood or broncho-alveolar lavage (BAL) or CMV disease and time to death Secondary: Time to CMV infection at other sites, time to development of CMV disease	Primary: Time to CMV infection in blood or BAL or CMV disease was significantly prolonged with valacyclovir compared to acyclovir (HR 0.59, 95% CI: 0.46 to 0.76, P<0.0001). Death rates did not differ between treatment groups (24% vs 25%, HR=0.68, 95% CI: 0.73 to 1.31, P=0.089). Secondary: Time to CMV infection in other sites was significantly prolonged with valacyclovir compared to acyclovir (HR=0.59, 95% CI: 0.45 to 0.71, P<0.0001). Time to definitive CMV disease episodes did not differ between the treatment groups (HR=0.71, 95% CI: 0.30 to 1.65, P=0.421). Time to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients initially received acyclovir IV 500 mg/m^2 from transplantation to day 28 or discharge			(definitive or presumed) and opportunistic infection	presumed CMV disease episodes did not differ between the treatment groups (HR=0.67, 95% CI: 0.33 to 1.36, P=0.269). The incidence of bacterial and/or fungal infections was comparable between treatment groups. Drug-related adverse events were comparable between treatment groups. The most commonly reported adverse events were nausea, vomiting, abdominal pain and diarrhea.
Amir et al.[99] (2010) Ganciclovir IV 5 mg/kg every 12 hours for 6 weeks, then valganciclovir PO (weight based) every 12 hours for 6 weeks, then once daily to age 1 year	RETRO Children with congenital CMV infection	N=23 12 months	Primary: Auditory function BSER (brainstem evoked response), adverse effects	Primary: Best ear was normal at birth in 65% of infants and was normal at ≥1 year in 85% of patients (P=0.365). In 26% of affected ears, an improvement in hearing was demonstrated. In the remaining, 72% had no change in hearing and 2% had a decrease in hearing. There was no difference in hearing outcomes in infants when compared to the short-term protocol tested by Kimberlin et al. (35-40% in each group had hearing defects). Of patients normal at baseline, 35% had a worsening in hearing at ≥1year in the Kimberlin study compared to no change in hearing in the 25 normal ears in the current study (P=0.001). Improvement occurred in 57% of current study patients compared to 39% in the Kimberlin study, (P=0.38). When number of ears was analyzed 76% had normal hearing compared to 35% in the Kimberlin group (P<0.001). The most frequent side effects were neutropenia and central line infections.
Studies of Ocular Complications of AIDS Research Group[48] (2001) Ganciclovir	RCT Patients with HIV with active CMV retinitis	N=61 34 months	Primary: Retinitis progression (new lesions that covered >25% of a standard disk area or movement of	Primary: Retinitis progression occurred at a rate of 0.67 per person/year in the ganciclovir group compared to 0.71 per person/year with cidofovir (P=0.72). Loss of visual acuity occurred at a rate of 0.78 per person/year in the ganciclovir group compared to 0.47 per person/year with cidofovir

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
surgically placed intraocular implant and ganciclovir 1,000 mg PO TID vs cidofovir IV 5 mg/kg once weekly for 2 doses, then 5 mg/kg every other week			border a pre-described length), loss of visual acuity of >15 letters and rate of loss of visual field Secondary: Serious ocular complications and mortality rates	(P=0.28). Visual field loss occurred at a rate of 7 degrees per month with ganciclovir compared to 2 degrees with cidofovir (P=0.048). Secondary: Vitreous hemorrhage was reported at a rate of 0.13 per person/year in the ganciclovir group compared to none with cidofovir (P=0.014). Uveitis was reported at a rate of 0.09 per person/year in the ganciclovir group compared of 0.35 per person/year in cidofovir (P=0.066). Mortality rates were 0.41 per person/year in the ganciclovir group compared to 0.49 per person/year with cidofovir (P=0.59).
Winston et al.[45] (2003) Ganciclovir IV 5 mg/kg every 12 hours for 1 week, then 6 mg/kg once daily for 5 days per week until day 100 after transplantation vs valacyclovir PO 2,000 mg QID until day 100 after transplantation All patients initially received acyclovir IV 500 mg/m^2 from transplantation to	DB, MC, RCT Patients age ≥13 years old that received an allogenic bone marrow transplant (BMT) seropositive for CMV antibody	N=168 100 days	Primary: Incidence of CMV infection, survival rates at 180 days, incidence of other herpesvirus infection, bacterial infection, fungal infection and incidence of neutropenia	Primary: CMV infection occurred in 12% of patients who received valacyclovir and 19% patients who received ganciclovir (HR=1.42, 95% CI: 0.391 to 2.778, P=0.934). HSV infections occurred in 4% of patients treated with valacyclovir and 5% taking ganciclovir. VZV infections developed in 2% of patients treated with valacyclovir and 1% taking ganciclovir. After 180 days, 47% of patients treated with valacyclovir and 36% taking ganciclovir died as a result of complications (HR=1.193, 95% CI:0.739 to 1.925, P=0.470). Bacterial infections occurred in 32% of patients treated with valacyclovir and 41% taking ganciclovir. Fungal infections occurred in 10% of patients treated with valacyclovir and 18% taking ganciclovir. Significantly less patients taking valacyclovir developed neutropenia compared to ganciclovir (13% vs 32%, P=0.007).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
engraftment.				
Pavlopoulou et al.[49] (2005) Ganciclovir 1,000 mg PO TID for 3 months vs valacyclovir 2,000 mg QID for 3 months	PRO, RCT Patients age ≥14 years who received a renal transplant	N=83 6 months	Primary: Occurrence of CMV infection or disease and drug-related adverse effects Secondary: Frequency of acute graft rejection, non-CMV infections, renal function and healthcare utilization	Primary: CMV infection occurred in 19% of patients on valacyclovir and 17.5% of patients taking ganciclovir. The difference was not significantly significant. No drug-related adverse events that could be attributed to either drug were recorded during the prophylaxis treatment stage. Secondary: Acute rejection episodes occurred in 11.6% with valacyclovir and 12.5% with ganciclovir. The difference was not significantly significant. Other herpesvirus infections occurred in 2% of patients on valacyclovir and 5% of patients taking ganciclovir. The difference was not significantly significant. Other nonviral infections occurred at a rate of 90% in the ganciclovir group compared to 53.5% with valacyclovir (P=0.003). The difference in infection rates was due to a higher incidence of urinary tract infections observed in the ganciclovir-treated patients (20 vs 10 with valacyclovir). Renal function did not differ between treatment groups. Use of medical inpatient and outpatient resources did not differ between treatment groups.
Paya et al.[46] (2004) Ganciclovir 1,000 mg TID until day 100 after transplantation vs valganciclovir PO 900 mg QD until	RCT Patients age ≥13 years old negative for CMV who received a solid organ transplant from a CMV positive donor (D+/R-)	N=372 100 days	Primary: Incidence of CMV infection after 6 months Secondary: Incidence of CMV viremia, incidence of acute graph rejection after CMV disease and graft loss	Primary: After 6 months, CMV infection occurred in 12.1% of patients who received valganciclovir and 15.2% in those taking ganciclovir (95% CI, –0.042 to 0.110). Secondary: The incidence of CMV viremia was comparable between treatment groups at 6 months (39.7% valganciclovir vs 43.2% ganciclovir) and at 12 months (48.5% valganciclovir vs 48.8% ganciclovir). The incidence of patients with ≥1 acute graft rejection episode was similar for both treatment groups at 6 and 12 months.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
day 100 after transplantation				Reported drug-related adverse events were comparable between treatment groups. The most commonly reported adverse events were diarrhea, tremor, graft rejection and headache.
Martin et al.[47] (2002) Ganciclovir IV 5 mg/kg BID for 3 weeks and then 5 mg/kg QD for 1 week vs valganciclovir PO 900 mg BID for 3 weeks then 900 mg QD for 1 week	RCT Adult HIV patients with newly diagnosed CMV retinitis	N=160 4 weeks	Primary: Progression of retinitis during the first four weeks Secondary: Proportion of patients achieving satisfactory response and time to progression to retinitis	Primary: After 4 weeks, 10% of patients on ganciclovir and 9.9% of patients on valganciclovir had progression of CMV retinitis (difference=0.1%, 95% CI, –9.7 to 10.0). Secondary: Satisfactory response to therapy was achieved in 77% of patients on ganciclovir and 71.9% of patients on valganciclovir (difference=5.2%, 95% CI:–20.4 to 10.1). Median time to progression of retinitis was 125 days with ganciclovir and 160 days with valganciclovir. Diarrhea was the most commonly reported adverse event and was reported in 19% of patients on valganciclovir compared to 10% of patients on ganciclovir (P=0.11). Neutropenia was reported with similar frequency between the two treatment groups.
Weclawiak et al.[95] (2010) Ganciclovir IV 10 mg/kg/day for 3 weeks vs valganciclovir (VGC) 900 mg/day for 3 months	RETRO Kidney transplant recipients who were CMV-seropositive	N=182 Mean 23-34 months	Primary: Incidence of CMV infection and disease, patient and graft survival at 1 and 2 years	Primary: There was a lower rate of CMV reactivation at 1 year in the VGC group compared to the ganciclovir preemptive group (28% vs 67.4%, respectively; P<0.001). At the end of follow-up, the respective incidences of CMV reactivation was 33.3% with VGC and 68.9% with ganciclovir (P<0.001). VGC therapy resulted in a longer time to CMV infection than ganciclovir (211 days vs 45 days, respectively; P<0.001). VGC prophylaxis resulted in a significantly lower overall incidence of CMV disease compared to ganciclovir treatment (2.68% vs 9.8%, respectively; P=0.021). The incidence of CMV disease within the first 100 days posttransplant was greater in the ganciclovir group compared to VGC (8.3% vs 0%, P=0.01). There was no difference 100 days posttransplant (2.68% with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				ganciclovir and 1.65% with VGC; P=NS). The long-term follow-up showed similar mortality rates among the treatment groups (3% with ganciclovir and 4.7% with VGC). At 1 year, 24.2% of patients from the prophylactic group had experienced at least one episode of acute allograft rejection compared to 25.3% of patients from the preemptive group (P=0.941). At the end of follow-up, the incidence of acute allograft rejection was 27.3% in the prophylactic group and 31.1% in the pre-emptive group (P=0.492).
Said et al.[81] (2007) Ganciclovir 5 mg/kg per day IV for 2 weeks (GAN) vs valganciclovir 900 mg orally per day for 2 weeks (VAL2w) vs valganciclovir 900 mg orally per day for 3 months (VAL3m)	RCT Kidney transplant recipients who were seropositive for CMV and who were receiving induction immuno-suppression	N=110 6 months	Primary: Onset of the disease, positive test for CMV, fever, leukopenia, systemic CMV manifestations, graft function, and rejection episodes	Primary: There was no statistical difference among the 3 groups in the incidence of acute rejection episodes or graft loss. There were 6 patients in the GAN group (14.6%) with CMV disease compared to 7 patients in the VAL2w group (30.4%) and 4 patients in VAL3m group (8.7%). The incidence of fever with a positive CMV test was significantly higher (P=0.035) in the VAL2w compared with the other 2 groups. In contrast, the incidence of leukopenia with negative CMV tests was significantly higher (P=0.040) in the VAL3m group compared with the GAN group and relatively similar to the VAL2w group. Serum creatinine was significantly higher in the VAL2w group at 3 and 6 months (P=0.011 and P=0.020, respectively) compared with the GAN group and at 1 month (P=0.049) in the VAL3m group compared with the GAN group.
Reischig et al.[92] (2008) Valacyclovir 2 g QID for 3 months	RCT Renal transplant recipients at risk for CMV	N=66 12 months	Primary: Incidence of CMV viremia and CMV disease, rate of acute rejection	Primary: The 12-month incidence of CMV viremia was higher in the preemptive group than the prophylaxis group (92% vs 59%, respectively; P<0.001). The incidence of CMV disease was not significantly different in the preemptive group compared to the prophylaxis group (6% vs 9%,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs valganciclovir 900 mg BID for at least 14 days				respectively; P=0.567). The onset of CMV viremia was delayed in the valacyclovir group compared to the valganciclovir group (37 days vs 187 days, respectively; P<0.001). There was a higher rate of biopsy-proven acute rejection in the preemptive group than in the prophylaxis group (36% vs 15%, respectively; P=0.034).
Leone et al.[96] (2010) Valacyclovir for 6 months vs valganciclovir for 6 months vs no prophylaxis	RETRO Kidney transplant recipients	N=550 Variable duration	Primary: Incidence of CMV disease, acute rejection; patient and graft survival, other infections, malignancies, hypertension diabetes	Primary: The incidence of CMV disease was highest with no prophylaxis (33.2%) and lowest in the valganciclovir prophylaxis group (8.6%; P<0.001). Valganciclovir prophylaxis had lower incidence of CMV during the first 6 months (37.5%) compared with valacyclovir (75%; P=0.018) and no prophylaxis (90.5%; P<0.01). Time to onset of posttransplant CMV was significantly longer in valganciclovir-treated patients (228 days) compared to no prophylaxis (33 days, P=0.044) and compared to valacyclovir (93 days; P=NS). There was no difference in episodes of graft rejection between valganciclovir (74.3%), valacyclovir (73.4%), and no prophylaxis groups (72.6%). There were fewer herpes viral infections in patients treated with valganciclovir (5.3%) compared to valacyclovir (15.5%; P=0.014) and compared to no prophylaxis (14.5%; P<0.001). There was no difference in incidence of malignancy between groups. There was a significantly lower proportion of patients with hypertension in patients treated with valganciclovir (25.7%) compared to valacyclovir (45.7%; P<0.001) and no prophylaxis (48.4%; P<0.001) There was a higher incidence of diabetes in the valganciclovir group (20.8%) compared to no prophylaxis (12.6%; P=0.032).
Asberg et al.[80]	RCT, OL, AC, MC	N=321	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2007) Valganciclovir 900 mg twice daily vs ganciclovir 5 mg/kg IV twice daily Both treatments were administered for an induction period of 21 days, followed by valganciclovir 900 mg daily until Day 49.	Adult solid organ transplant recipients with CMV disease	49 days	Treatment success (defined as the eradication of CMV viremia at Day 21) Secondary: Clinical assessment of CMV disease activity, time to viremia below the limit of detection (<200 copies/mL), viral load kinetics and safety and tolerability	In the intention-to-treat population, viral eradication (<600 copies/mL) was achieved in 45.1% of the valganciclovir-treated patients and in 48.4% of the ganciclovir-treated patients at Day 21 (95% CI –14.0 to +8.0%). Viral eradication at Day 49 was 67.1% in valganciclovir- and 70.1% in ganciclovir-treated patients (P=NS). Secondary: Clinical resolution of CMV disease occurred at a mean of 15.1 days (95% CI 13.0–17.2) and 15.1 days (95% CI 13.0–17.3) for the valganciclovir and ganciclovir groups, respectively (P=0.880). At Day 21, clinical success was achieved in 127 of 164 valganciclovir-treated patients (77.4%) and 126 of 157 patients (80.3%) in the IV ganciclovir arm; by Day 49 clinical success was achieved in 140 of 164 patients (85.4%) and 132 of 157 patients (84.1%), respectively. Resolution of fever and disappearance of active disease occurred at similar time points in both arms. Median baseline viral loads were not different between the groups. Viral clearance (<600 copies/mL) at Day 21 was achieved in 74 of 133 patients (55.6%) in the valganciclovir group and 76 of 126 patients in the ganciclovir group (60.3%; P=NS), and increased to 110 of 133 patients (82.7%) and 110 of 126 patients (87.3%), respectively, at Day 49 (P=NS). The mean time to a clinically relevant drop in viral load (≥0.3 natural log units) was 6.1 ± 4.5 days (N=120) for valganciclovir and 6.6 ± 4.7 days for ganciclovir (P=NS). Median times to viral eradication using either the 600 copies or 200 copies cutoff were similar in both arms. The median viral load half-life was 11.5 days (8.3–16.5 days) and 10.4 days (7.9–14.5 days) for valganciclovir- and ganciclovir-treated patients, respectively (P=0.932).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				During the first 21 days, treatment was discontinued in11 (6.7%) valganciclovir versus 7 (4.5%) ganciclovir patients, respectively (P=NS). There were no major differences in the frequencies of adverse events between the treatment groups.
Shiley et al.[91] (2009) Valganciclovir 900 mg daily vs ganciclovir 1,000 mg PO TID or ganciclovir 6 mg/kg/day IV Prophylaxis was continued for the first 100 days after transplantation.	RETRO Orthotopic liver transplant patients at high risk for CMV	N=66 Variable duration	Primary: Development of CMV disease Secondary: Mortality, rejection episodes, other infections	Primary: The incidence of CMV was 12.1%, with the mean number of days to onset of 190. A total of 22% of valganciclovir patients developed CMV compared to 5.1% of patients receiving ganciclovir (P=0.056). Secondary: A total of 15% of patients died, but no deaths were attributable to CMV disease. There was a higher incidence of rejection in patients who developed CMV (50%; RR, 10; P=0.0025). The incidence of other infections was similar between the treatment groups (P=0.19). Other infections occurred more frequently in patients that developed CMV (62.5%) versus those that did not (36.7%). However, this trend did not reach statistical significance (P=0.11).
Lapidus-Krol et al.[98] (2010) Valganciclovir PO up to 900 mg/day vs ganciclovir PO 30 mg/kg/dose up to 1g/dose TID Treatment was given for 3 months	RETRO Children who underwent kidney or liver transplant	N=92 12 months	Primary: Symptomatic or tissue invasive CMV, safety	Primary: The overall incidence of CMV episode was 13.7% in valganciclovir-treated patients and 19.5% in ganciclovir-treated patients (P=0.573). The overall time to CMV infection was not different among the treatment groups (P=0.46). Rates of acute allograft rejection were similar in valganciclovir-treated patients compared to ganciclovir-treated patients (25% vs 34%, respectively; P=NS) and between patients with CMV infection compared to noninfected patients (40% vs 27.3%, respectively; P=NS). There was no difference in adverse events between valganciclovir and ganciclovir.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
in R+/D+ or R+/D- recipients and for 6 months in R-/D+.				
Palmer et al.[90] (2010) Valganciclovir 900 mg once daily for 3 months vs valganciclovir 900 mg once daily for 12 months	PRO, RCT, DB, PC Adults receiving their first lung transplant who were at risk for CMV	N=136 13 months posttransplant	Primary: CMV end-organ disease Secondary: CMV disease severity, CMV infection, acute rejection, opportunistic infections, ganciclovir resistance and safety	Primary: Patients treated with short-course valganciclovir had a greater incidence of CMV disease (32%) compared to patients in the extended-course group (4%; P<0.001). Secondary: There was a significant reduction in disease severity with extended-course valganciclovir compared to short-course valganciclovir (110, 000 vs 3,200 copies/ml, respectively; P=0.009). There was a significant reduction in CMV infection with extended-course valganciclovir compared to short-course valganciclovir (64% vs 10%, respectively; P<0.001) There was no difference in rates of acute rejection, opportunistic infections, adverse events, resistance or adverse events between the two groups.
Kalil et al.[89] (2011) Valganciclovir 900 mg daily (VGC) vs valganciclovir 450 mg daily (VGC) vs ganciclovir 3 g/day, valacyclovir 3-8 g/day or preemptive therapy	MA Valganciclovir use for CMV prevention in any type of solid organ transplant	N=3,074 (20 trials) Variable duration	Primary: Prevention of CMV disease Secondary: Leukopenia and neutropenia risk; risk of allograft rejection, loss and death	Primary: <u>Valganciclovir 900 mg daily versus controls</u> The risk of developing CMV disease was 1.06 with VGC 900 mg versus controls (P=0.812). There was no difference in the subgroup analysis of types of controls (ganciclovir or preemptive therapy) or type of organ transplant. The risk of leukopenia was 5.24 for VGC 900 mg versus controls a (P=0.0004). The risk for acute allograft rejection was 1.71 for VGC 900 mg versus controls (P=0.43). The risk of neutropenia was higher with 900 mg VGC compared to controls (RR, 3.72; P=0.002). The risk of allograft rejection, allograft loss and death was not significantly higher with VGC 900 mg compared to control.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(controls)				<u>Valganciclovir 450 mg daily versus controls</u> The risk of developing CMV disease was 0.77 with VGC 450 mg versus control (P=0.23). There was no difference in the subgroup analysis of types of controls (ganciclovir or preemptive therapy) or type of organ transplant. The risk of leukopenia was 1.58 for VGC 450 mg versus controls (P=0.07). The risk for acute allograft rejection was 0.80 for VGC 450 mg versus controls (P=0.34). The risk of neutropenia was 2.92 with VGC 450 mg versus controls (P=0.002). The risk of allograft rejection, allograft loss and death was not significantly higher with VGC 450 mg compared to control. <u>Valganciclovir 900 mg versus valganciclovir 450 mg</u> Adjusted comparison of VGC 900 mg vs VGC 450 mg showed there was an increased risk of leukopenia in the VGC 900 mg group (OR, 3.32; P=0.0005). Risk of neutropenia between VGC 900 mg and 450 mg could not be conducted due to differing definitions in the literature. Adjusted comparison of VGC 900 mg vs VGC 450 mg showed there was an increased risk of allograft rejection in the VGC 900 mg group (OR, 2.56; P=0.0005). There was no difference in risk between treatment groups for death or allograft loss.
Hodson et al.[83] (2008) Antiviral	MA Solid organ transplant recipients	N=3,737 (32 trials) Variable	Primary: Incidence of CMV disease and CMV infection; all-cause	Primary: <u>Overall</u> Prophylaxis with all agents significantly reduced the risk for CMV disease overall (RR 0.42, 95% CI 0.34 to 0.52), CMV syndrome (RR 0.41, 95%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
medications (acyclovir, ganciclovir, valacyclovir, valganciclovir) vs placebo or no treatment	who received antiviral therapy for CMV prophylaxis	duration	mortality	CI 0.29 to 0.57) and CMV invasive organ disease (RR 0.34, 95% CI 0.21 to 0.55) compared with placebo or no treatment. The average risk of CMV infection in the placebo/no treatment arms was 49% (range 36% to 100%). Prophylaxis significantly reduced CMV infection (RR 0.61, 95% CI 0.48 to 0.77). The treatment efficacy did not vary according to antiviral medication used on sub group analysis. When analyzed separately acyclovir (RR 0.45, 95% CI 0.29 to 0.69), ganciclovir (RR 0.44, 95% CI 0.34 to 0.58) and valacyclovir (RR 0.30, 95% CI 0.19 to 0.49) significantly reduced the risk for CMV disease compared with placebo or no treatment. The average all-cause mortality rate reported at one year or less post-transplant in the placebo/no treatment arms of all studies was 7.1% (range 0% to 37%). Prophylaxis significantly reduced all cause mortality (RR 0.63, 95% CI 0.43 to 0.92). <u>Ganciclovir versus acyclovir</u> In head-to-head studies, ganciclovir was more effective than acyclovir in preventing CMV disease in all recipients (RR 0.37, 95% CI 0.23 to 0.60), in CMV positive recipients (RR 0.27, 95% CI 0.13 to 0.55) and in CMV negative recipients of CMV positive organs (RR 0.64, 95% CI 0.41 to 0.99). There were no significant differences in the risk of death due to CMV disease (RR 0.33, 95% CI 0.07 to 1.58,) or all-cause mortality (RR 1.13, 95% CI 0.82 to 1.58). <u>Valganciclovir versus ganciclovir</u> Valganciclovir and ganciclovir were not significantly different in the prevention of CMV disease at six months or one year post-transplant. There were no significant differences at six months and one year in the prevention of CMV syndrome and CMV invasive organ disease. There were no significant differences at six months and one year in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				prevention of CMV infection. No significant differences were detected between medications in death due to CMV disease or all-cause mortality. <u>Valacyclovir versus ganciclovir</u> The risk of CMV disease and CMV infection did not differ significantly with valacyclovir compared with ganciclovir prophylaxis. No significant differences were detected in all-cause mortality. <u>Prophylaxis with different regimens of ganciclovir</u> No significant differences were detected in CMV disease, CMV syndrome, CMV invasive tissue disease or CMV infection when ganciclovir was administered daily vs three times weekly. No difference in all-cause mortality was detected. No significant differences were detected in CMV disease, CMV syndrome, CMV invasive tissue disease or CMV infection when comparing oral vs IV ganciclovir. There was no difference in all-cause mortality.
Hepatitis B				
Vassiliadis et al.[104] (2010) Adefovir 10 mg once daily plus lamivudine 100 mg daily vs adefovir 10 mg once daily	PRO, RCT Adult patients with HBeAg (-) chronic hepatitis B receiving lamivudine with documented genotypic resistance to lamivudine	N=60 20-60 months	Primary: Virologic response and normalization of ALT levels Secondary: Rate of resistance	Primary: Virologic response in the combination group was not significantly different than the adefovir monotherapy group (84.4% vs 73.3%; P=0.56). Mean virologic response was 8 months in both groups (P=0.18). At 48 months, the proportion of patients with undetectable HBV-DNA was higher in the combination therapy group than in the monotherapy group (88.9% vs 46.7%; P=0.009). Normalization of ALT levels was higher in the combination group compared to the monotherapy group (90.9% vs 57.1%; P=0.01). At 36 and 48 months, the proportion of patients with normalized ALT levels was higher in the combination group than in the monotherapy group (97.2% vs 53.3%; P<0.001 and 100% vs 53.3%; P<0.001, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				All patients treated with combination therapy had sustained undetectable HBV-DNA; four of 11 patients treated with monotherapy had breakthrough (34%; P<0.001). A total of 4.4% of patients in the combination group had emergence of adefovir resistance vs 40% of patients in the monotherapy group (P<0.001). Resistance in both groups occurred more frequently in those patients that did not achieve a virologic response. There was no difference in adverse events between the groups.
Sun et al.[108] (2011) Adefovir 10 mg daily x 72 weeks vs peginterferon alfa-2a 180 mcg/week x 48 weeks	OL, RCT Adult patients with chronic hepatitis B with lamivudine resistance	N=235 6 months posttreatment	Primary: Rate of HBeAg seroconversion at week 72	Primary: At 6 months posttreatment, significantly more patients in the peginterferon group achieved HBeAg seroconversion compared to adefovir (14.6% vs 3.8%, P=0.01). Overall, the response rate for all patients with lamivudine-resistant HBV was very low at any time period during the study. Patients taking peginterferon alfa-2a experienced a serious adverse event rate of 7.8% compared to 2.4% in the adefovir-treated group.
Pessôa et al.[103] (2008) Entecavir 1 mg/day for 24 weeks vs placebo for 24 weeks All patients continued lamivudine (300	PRO, RCT, DB, PC HIV/HBV co-infected patients >16 years of age with no evidence of hepatitis C or D, currently on lamivudine containing HAART for ≥24 weeks prior to enrollment or infected with lamivudine-resistant-associated	N=68 48 weeks	Primary: Mean change from baseline in HBV DNA at 24weeks Secondary: Mean change in serum HBV DNA adjusted from baseline at 48wks; proportion of patients with HBV-DNA <300 copies/mL at 24 and 48weeks; ALT	Primary: At 24 weeks, the mean HBV-DNA for entecavir-treated patients was 5.52 log_{10} compared to 9.27 log_{10} in patients receiving placebo. The mean change from baseline in entecavir-treated patients was -3.65 log_{10} copies/mL vs +0.11 log_{10} copies/mL for placebo (95% CI, -4.49 to -3.04; P<0.0001). Secondary: At 48 weeks, the mean HBV-DNA for entecavir-treated patients was 4.97log_{10} compared to 5.63 log_{10} in patients receiving placebo. The mean HBV-DNA change from baseline was -4.2 log_{10} in patients receiving entecavir from start of study. The mean HBV-DNA change from baseline was -3.65 log_{10} in patients randomized to placebo at the start of study who crossed over to open-label entecavir.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg QID)-containing HAART regimens. OL entecavir was allowed after 24 weeks.	HBV		normalization; proportion of patients with seroconversion; adverse events	ALT normalization occurred in 34% of entecavir-treated patients compared to 8% in placebo-treated patients (P=0.08). Loss of HBeAg occurred in 1 entecavir patient by week 48, but in no placebo treated patients (P=0.56). At week 24, HBeAg seroconversion occurred in 1 patient in the entecavir group. There were similar frequencies of adverse events in the entecavir (86%) and placebo (82%) groups. Headache and nasopharyngitis were the most common reported adverse events in both groups. There was no change to CD4 cell counts or HIV RNA levels.
Leung et al.[77] (2009) Entecavir (ETV) 0.5 mg daily for 52 weeks vs adefovir (ADV) 10 mg daily for 52 weeks	RCT, OL Patients ≥16 years of age, had HBeAg-positive chronic hepatitis B infection, compensated liver disease with a serum alanine aminotransferase (ALT) level between 1.3 and 10 times the upper limit of normal, and had never received treatment with nucleosides or nucleotides with activity against HBV	N=132 52 weeks	Primary: Mean reduction in serum HBV DNA by polymerase chain reaction (PCR) assay at week 12 Secondary: Mean change in HBV DNA from baseline to weeks 24 and 48; proportion of patients with undetectable serum HBV DNA (<300 copies/mL) at weeks 12, 24, and 48; proportion of patients with normalization of serum ALT; HBe	Primary: The mean reduction in serum HBV DNA level at week 12 was significantly greater in patients randomized to ETV compared with ADV (-6.23 versus -4.42 $\log_{10}$ copies/mL; P<0.0001). Secondary: The mean decrease in serum HBV DNA levels was greater with ETV than ADV at weeks 2, 4, 8, 24, and 48. The proportion of patients with HBV DNA of <300 copies/mL was higher in patients treated with ETV than in those treated with ADV at weeks 12, 24, and 48. At week 24, 15 ETV-treated patients (45%) and four ADV-treated patients (13%) achieved HBV DNA <300 copies/mL At week 48, 19 ETV-treated patients (58%) and six ADV-treated patients (19%) achieved HBV DNA <300 copies/ml. Normalization of serum ALT was documented in 25 (76%) ETV-treated patients and 20 (63%) ADV-treated patients at week 48. HBeAg loss and HBe seroconversion rates were similar for both ETV-treated and ADV-treated patients. For ETV-treated patients, HBeAg loss and HBe seroconversion rates were 6 of 33 (18%) and 5 of 33 (15%), respectively, versus 7 of 32 (22%) and 7 of 32 (22%), respectively, for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			seroconversion at week 48; and safety	ADV-treated patients (P=NS). Treatment was generally safe and well tolerated.
Zhao et al.[88] (2011) Entecavir 0.5 mg daily vs adefovir 10 mg daily	MA Nucleoside naïve, HBeAg (+), Asian patients treated with either entecavir or adefovir	N=267 (6 trials) 48 weeks	Primary: Efficacy at 48 weeks	Primary: The rate of undetected serum HBV-DNA was significantly higher in entecavir-treated patients versus adefovir therapy (RR, 1.73; 95% CI, 1.38-2.17; P<0.0001). The rate of ALT normalization was significantly higher in the entecavir-treated patients versus adefovir therapy (RR, 1.25; 95% CI, 1.06-1.49; P<0.009). The rate of HBeAg clearance was not significantly different in entecavir-treated patients versus adefovir therapy (RR, 0.77; 95% CI, 0.4-1.35; P=0.36). The rate of HBeAg seroconversion was not significantly different in entecavir-treated patients versus adefovir therapy (RR, 0.74; 95% CI, 0.28-1.94; P=0.53).
Chang et al.[59] (2006) <u>ETV-022</u> Entecavir 0.5 mg/day vs lamivudine 100 mg/day	RCT, DB Adult patients with HBeAg-positive chronic hepatitis B who had not previously been treated with a nucleoside analogue	N=715 52 weeks	Primary: Histologic improvement after 48 weeks of treatment Secondary: Serum HBV-DNA at 48 weeks, HBeAg status, decrease in Ishak fibrosis score, and ALT	Primary: After 48 weeks, a histologic response was demonstrated in 72% of entecavir-treated patients and 62% lamivudine-treated patients (P=0.009). Secondary: Significantly more patients had undetectable serum HBV DNA while on entecavir compared to lamivudine (67% vs 36%; P<0.001). HBeAg loss occurred in 22% of entecavir-treated patients and 20% of those treated with lamivudine (P=0.45). HBeAg seroconversion occurred in 21% of entecavir-treated patients and 18% of those treated with lamivudine (P=0.33). Significantly more patients had normalization of ALT while on entecavir compared to lamivudine (68% vs 60%; P=0.02). The frequency and severity of adverse drug events were comparable between treatment groups. The most commonly reported adverse events

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				were headache, upper respiratory tract infection, nasopharyngitis, cough, pyrexia, upper abdominal pain, fatigue, and diarrhea.
Chang et al.[105] (2009) ETV-022 Entecavir 0.5 mg/day vs lamivudine 100 mg/day ETV-901 Entecavir 0.5 to 1 mg/day ± lamivudine	RCT, DB Adult patients with HBeAg-positive chronic hepatitis B who had not previously been treated with a nucleoside analogue	N=407 96 weeks	Primary: Serum HBV-DNA, HBeAg status, ALT, safety	Primary: A total of 64% of entecavir-treated patients had HBV-DNA<300 copies/mL at week 48, which increased to 74% at the end of dosing. A total of 66% of entecavir-treated patients had ALT normalization at 48 weeks, which increased to 79% at the end of dosing in year 2. A total of 40% of lamivudine-treated patients had HBV-DNA <300 copies/mL at week 48, which decreased to 37% at the end of dosing. A total of 71% of lamivudine-treated patients had ALT normalization at 48 weeks, which decreased to 68% at the end of dosing in year 2. At the end of dosing, 11% of entecavir-treated patients and 12% of lamivudine-treated patients experienced HBe seroconversion. Cumulative confirmed ALT normalization was achieved in 87% and 79% of entecavir and lamivudine treated patients, respectively (P<0.0056). Cumulative confirmed HBV-DNA <300 copies/mL was achieved in 80% of entecavir-treated patients compared to 39% of lamivudine-treated patients at 2 years (P<0.001). The proportion of patients experiencing HBe seroconversion (31% vs 25%), HBsAg loss (5% vs 3%) and HBsAg seroconversion (2% vs 2%) did not different significantly among the treatment groups. Through 2 years of therapy headache (10% with entecavir and 8% with lamivudine), fatigue (6% with entecavir and 5% with lamivudine), and increased ALT levels (4% with entecavir and 7% with lamivudine) were the most common adverse events reported.
Chang et al.[106] (2010) ETV-022 Entecavir 0.5 mg/day	RCT, DB Adult patients with HBeAg-positive chronic hepatitis B who had not	N=146 240 weeks	Primary: Serum HBV-DNA, HBeAg status, ALT, safety	Primary: At year 1, 55% of patients achieved HBV DNA <300 copies/mL, which increased to 83% at year 2, and 94% at year 5. A total of 65% of patients achieved ALT normalization at 1 year, 78% at 2 years, and 80% at year 5. At year 5, the mean ALT level for the entecavir

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vs lamivudine 100 mg/day ETV-901 Entecavir 0.5 to 1 mg/day ± lamivudine	previously been treated with a nucleoside analogue			group was 33 IU/L, a decrease from the mean level of 122 IU/L at baseline. At year 2, 31% of patients achieved HBeAg seroconversion and 5% of patients achieved HBsAg loss. These patients were not enrolled into ETV-901. Of the 141 patients enrolled in ETV-901, 23% achieved HBeAg seroconversion and 1.4% achieved HBsAg loss during ETV-901. One patient developed entecavir resistance that emerged at year 3. No patient discontinued therapy due to an adverse event in ETV-901. A total of 16% had a grade 3/4 adverse event; 20% had a serious adverse event; 5% experienced death.
Lai et al.[60] (2006) Entecavir 0.5 mg once daily vs lamivudine 100 mg once daily	DB, RCT Adult patients with HBeAg-negative hepatitis B not previously treated with a nucleoside analogue	N=648 52 weeks	Primary: Histologic improvement at week 48 Secondary: Reduction in HBV DNA level and ALT normalization	Primary: After 48 weeks, a histologic response was demonstrated in 70% of entecavir-treated patients and 61% lamivudine-treated patients (P=0.01). Secondary: Significantly more patients had undetectable serum HBV DNA while on entecavir compared to the number of those on lamivudine with undetectable serum HBV DNA (90% vs 72%; P<0.001). Significantly more patients had normalization of ALT while on entecavir compared to lamivudine (78% vs 71%; P=0.045). The frequency and severity of adverse drug events was comparable between treatment groups. The most commonly reported adverse events were headache, upper respiratory tract infection, upper abdominal pain, influenza, nasopharyngitis, dyspepsia, fatigue, back pain, arthralgia, diarrhea, insomnia, cough, nausea, and myalgia.
Gish et al.[78] (2007) Entecavir 0.5 mg once daily vs	RCT, DB Adult patients with HBeAg-negative hepatitis B not previously treated with a nucleoside	N=407 96 weeks	Primary: Proportions of patients with HBV DNA levels <300 copies/mL by polymerase chain reaction (PCR),	Primary: For all treated patients, the cumulative analysis showed that a higher proportion of entecavir-treated than lamivudine-treated patients achieved confirmed HBV DNA levels <300 copies/mL by PCR assay through 96 weeks of treatment (entecavir 80% and lamivudine 39%; P<0.0001). Through 96 weeks of therapy, for all treated patients, a higher cumulative

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
lamivudine 100 mg once daily	analogue		normalization of ALT levels, and HBeAg seroconversion at the end of dosing (up to 96 weeks)	proportion of entecavir- treated (87%) than lamivudine-treated (79%) patients achieved confirmed normalization of ALT levels (P<.0056). Through 96 weeks of treatment and 6 months of post-treatment follow-up, 5% of entecavir-treated and 3% of lamivudine-treated patients achieved confirmed HBsAg loss, and 2% of patients in both treatment groups achieved seroconversion to antibody to hepatitis B surface antigen. Over the course of 2 years of treatment, 31% of entecavir-treated patients and 26% of lamivudine-treated patients became responders. Fewer entecavir-treated (8%) than lamivudine-treated (41%) patients were nonresponders during this 96-week period. The frequency of on-treatment adverse events was comparable (entecavir, 87%; lamivudine, 84%). Serious adverse events on-treatment occurred in 8% of patients in both treatment groups.
Sherman et al.[101] (2006) Entecavir 1 mg daily vs lamivudine 100 mg daily	RCT, DB, AC HBsAg (+) patients ≥16 years of age who were receiving ongoing lamivudine therapy and were refractory to that therapy	N=286 52 weeks	Primary: Histologic improvement and composite endpoint (HBV-DNA <0.7 mEq/ml and ALT <1.25 times the upper limit of normal), virologic endpoints, serologic endpoints, biochemical endpoints	Primary: Histologic improvement occurred in 55% of patients treated with entecavir compared to 28% of patients treated with lamivudine (P<0.0001). A total of 34% of entecavir patients and 16% of lamivudine patients had improvement in Ishak fibrosis scores (P=0.0019). A total of 55% of patients treated with entecavir reached the composite endpoint compared to 4% of lamivudine patients (P=0.001). A total of 9% of entecavir-treated patients and <1% of lamivudine-treated patients achieved combined HBV-DNA <0.7 mEq/mL and loss of HBeAg at 48 weeks (P=0.008). Mean changes from baseline in HBV-DNA was -5.11 $\log_{10}$ copies/mL in entecavir-treated patients versus -0.48 $\log_{10}$ copies in lamivudine-treated patients (P<0.001). The proportion of patients achieving HBV-DNA <300 copies/mL at 48 weeks was higher in entecavir-treated patients (19%) compared to lamivudine-treated patients (1%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Loss of HBeAg occurred more frequently in entecavir patients compared to lamivudine patients (10% vs 3%, respectively; P<0.0278). HBeAg seroconversion was not significantly different between entecavir patients (8%) and lamivudine patients (3%; P=0.06). More entecavir- treated patients achieved ALT normalization compared to lamivudine-treated patients (61% vs 15%, respectively; P<0.0001).
Chan et al.[74] (2007) Telbivudine 600 mg daily for 52 weeks (group A) vs adefovir 10 mg daily for 52 weeks (group B) vs adefovir 10 mg daily for 24 weeks followed by telbivudine 600 mg daily for the remaining 28 weeks (group C)	RCT, OL Patients 18-70 years of age with chronic hepatitis B and no history or signs of hepatic decompensation, positivity for serum hepatitis B surface antigen (HBsAg), positivity for serum HBeAg, serum alanine aminotransferase (ALT) level between 1.3 and 10 times the upper limit of normal, and serum HBV DNA levels of at least 6 log_{10} copies/mL	N=136 52 weeks	Primary: HBV DNA reduction from baseline values at week 24 Secondary: HBV DNA reduction from baseline values at week 52, comparisons of mean residual HBV DNA levels, proportions of patients with HBV DNA who were PCR-negative or had HBV DNA values less than 5, 4, or 3 log_{10} copies/mL; serum ALT normalization; HBeAg loss and seroconversion; HBsAg loss and seroconversion;	Primary: At week 24, the reduction in mean serum HBV DNA level from baseline in group A differed from that in pooled groups B and C (-6.30 vs -4.97 log_{10} copies/mL; P<0.001), as did the proportion of patients whose serum HBV DNA levels were undetectable by PCR (39% vs 12%; P<0.001). Serum HBV DNA levels remained at or above 5 log_{10} copies/mL in more adefovir recipients than telbivudine recipients (42% vs 5%; P<0.001). Group A and pooled groups B and C differed in the proportions of patients with HBV DNA levels that remained at or above 3 log_{10} copies/mL (50% vs 78%; P<0.003) and 4 log_{10} copies/mL (32% vs 61%; P<0.003). Secondary: In patients switched from adefovir to telbivudine at week 24 (group C), mean HBV DNA levels rapidly decreased by approximately 1.4 log_{10} copies/mL after week 24; within 8 weeks, they were nearly identical to levels in patients in group A. An increase in HBeAg seroconversion was seen in group C, although the differences were not statistically significant. At week 52, mean residual HBV DNA levels in groups A and C differed from those in group B (3.01 log_{10} copies/mL and 3.02 log_{10} copies/mL, respectively, vs 4.00 log_{10} copies/mL; P<0.004). Reductions of mean serum HBV DNA levels were greater in groups A and C (-6.56 and -6.44 log_{10} copies/mL, respectively) than in group B (-5.99

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and primary treatment failure	log_{10} copies/mL; P=0.18 and P=0.28, respectively). More patients in groups A and C than in group B were PCR-negative at week 52, although these differences did not reach statistical significance (60% and 54% vs 40%; P=0.07 and P=0.20, respectively). The rate of primary treatment failure (HBV DNA levels remaining >5 log_{10} copies/mL through week 52) in group B (29%) also differed from that in group A (2%; P<0.008) and in group C (11%; P=0.042). Loss of HBeAg was more common in group A than in pooled groups B and C at week 24, and was more common in groups A and C at week 52 (30% and 26%, respectively) than in group B (21%), although intergroup differences were not statistically significant. No patient experienced HBsAg loss or seroconversion. At week 52, ALT normalization occurred in 79% of patients in group A and 85% of patients in group C, compared with 85% of those in group B (P=0.45 and P=0.98, respectively).
Zheng et al.[86] (2010) Telbivudine 600 mg daily vs entecavir 0.5 mg daily	PRO, RCT, OL, PG Adult Chinese patients with previously untreated HbeAg-positive HBV	N=131 24 weeks	Primary: Mean reduction in HBV-DNA copies at 24 weeks Secondary: Mean reduction in HBV-DNA at 12 weeks, absence of HBV-DNA; absence of HBeAg, HBeAg seroconversion, normalization of ALT, adverse events	Primary: Mean reductions in HBV-DNA from baseline at week 24 were not significantly different between the telbivudine and entecavir groups (6.00 vs 5.80 log_{10}, respectively). Secondary: Mean reductions in HBV-DNA from baseline at 12weeks were not significantly different between the telbivudine and entecavir groups (4.99 vs 4.69 log_{10}, respectively). There was no significant difference in undetectable HBV-DNA at 12 weeks between the telbivudine and entecavir groups (43.1% vs 34.8%, respectively; P=0.334). There was no significant difference in undetectable HBV-DNA at 24 weeks between the telbivudine and entecavir groups (67.7% vs 57.6%, respectively; P=0.232).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				At 12 weeks, there were higher rates of HBeAg absence (20% vs 3%; P=0.002) and seroconversion (13.8% vs 3%; P=0.03) in the telbivudine group compared to entecavir group, respectively. At 24 weeks, there was no significant difference in rates of HBeAg absence (36.9% vs 28.8%) or seroconversion (24.6% vs 13.6%) in the telbivudine group compared to entecavir group, respectively. There was no difference in normalization of ALT levels at 24 weeks in the telbivudine and entecavir groups (78.5% vs 74.2%; respectively). Adverse events were similar between each group with the most common being upper respiratory tract infection, fatigue, diarrhea, and coughing.
Lai et al.[73] (2007) Telbivudine 600 mg once daily vs lamivudine 100 mg once daily	RCT, DB, MC Adults aged 16–70 years with HBeAg-positive or HBeAg-negative chronic hepatitis B and compensated liver disease	N=1,370 52 weeks	Primary: Therapeutic response (defined as reduction of serum HBV DNA levels to <5 $\log_{10}$ copies/mL and normalization of ALT level or loss of serum HbeAg) Secondary: Proportion of patients with HBV DNA non-detectable (<300 copies/mL), HbeAg loss, normalization of serum ALT level	Primary: Reduction in serum HBV DNA levels at week 52 was significantly greater in the telbivudine group than in the lamivudine group. The difference was evident by week 12 in HBeAg-positive patients (reductions of 5.71 $\log_{10}$ copies per milliliter for telbivudine and 5.42 $\log_{10}$ copies per milliliter for lamivudine, P=0.01) and by week 8 in HBeAg-negative patients (reductions of 4.36 $\log_{10}$ copies per milliliter for telbivudine and 4.08 $\log_{10}$ copies per milliliter for lamivudine, P=0.02), and it persisted through week 52. Secondary: At week 52, the proportion of patients in whom serum HBV DNA levels were undetectable by PCR assay was significantly greater in the telbivudine group than in the lamivudine group among HBeAg-positive patients (60.0% vs 40.4%, P<0.001) and HBeAg-negative patients (88.3% vs 71.4%, P<0.001). The mean time required for serum HBV DNA to become undetectable by PCR assay was significantly shorter in the telbivudine group than in the lamivudine group among HBeAg-positive patients (34 weeks vs 39 weeks, P<0.001) and HBeAg-negative patients (20 weeks vs 26 weeks, P<0.001). Primary treatment failure was less frequent with telbivudine than with lamivudine among both HbeAg-positive and HBeAg-negative patients, but the difference was significant only for HBeAg-positive patients.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Among HBeAg-positive patients, 25.7% of those in the telbivudine group and 23.3% of those in the lamivudine group had HBeAg loss (P=0.40) and 22.5% of those in the telbivudine group and 21.5% of those in the lamivudine group had HBeAg seroconversion (P=0.73). The rates of normalization of serum alanine aminotransferase at week 52 were high (levels more than 70%) in both treatment groups, with results meeting non-inferiority criteria in the HbeAg-positive and in the HBeAg-negative subgroups. The frequencies of adverse events through week 52 were similar for patients who received telbivudine and for those who received lamivudine. Serious adverse events were reported for 18 patients in the telbivudine group (2.6%) and 33 in the lamivudine group (4.8%).
Hou et al.[72] (2008) Telbivudine 600 mg once daily vs lamivudine 100 mg once daily	RCT, DB, MC Chinese adults aged 16–70 years with HBeAg-positive or HBeAg-negative chronic hepatitis B and compensated liver disease	N=332 52 weeks	Primary: Therapeutic response (defined as reduction of serum HBV DNA levels to <5 $\log_{10}$ copies/mL and normalization of ALT level or loss of serum HbeAg) Secondary: Serum HBV DNA changes from baseline, proportion of patients with HBV DNA non-detectable (<300 copies/mL), HbeAg loss and seroconversion,	Primary: <u>HBeAg-Positive Patients</u> Telbivudine resulted in a greater reduction in serum HBV DNA levels, compared with lamivudine. This difference in HBV DNA suppression was significant by week 8 and continued through week 52. <u>HBeAg-Negative Patients</u> Telbivudine produced a greater mean reduction of serum HBV DNA (5.5 $\log_{10}$ for telbivudine versus 4.8 $\log_{10}$ for lamivudine). However, these efficacy differences were not analyzed statistically because of the limited power for statistical comparisons within the small HBeAg-negative patient population. Secondary: <u>HBeAg-Positive Patients</u> At week 52, serum HBV DNA reduction from baseline was significantly greater for telbivudine (6.3 $\log_{10}$) than lamivudine (5.5 $\log_{10}$; P<0.001). Serum HBV DNA became PCR-negative (<300 copies/mL) more rapidly in telbivudine-treated patients and PCR negativity at week 52 was significantly more frequent with telbivudine treatment compared to lamivudine (67% versus 38%, P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			normalization of serum ALT level	The proportion of patients with primary treatment failure (serum HBV DNA remained above 5 log_{10} copies/mL throughout the 52 weeks of treatment) was significantly lower with telbivudine compared to lamivudine (4% versus 18%, P<0.001). Therapeutic response was significantly more common in the telbivudine group (85%) compared with lamivudine (62%; P<0.001), and serum ALT levels were normalized in 87% of telbivudine recipients versus 75% of lamivudine recipients (P<0.007). HBeAg loss was significantly more frequent in the telbivudine group compared with lamivudine (31% versus 20%, P<0.047). HBeAg seroconversion was more frequent with telbivudine (25%) compared with lamivudine (18%), but this difference was not statistically significant (P=0.14). No patient experienced HBsAg loss or seroconversion. <u>HBeAg-Negative Patients</u> Telbivudine as compared to lamivudine produced higher rates of therapeutic response (100% versus 82%), ALT normalization (100% versus 78%), and PCR-negative HBV DNA (85% versus 77%), and less primary treatment failure (0% for telbivudine versus 5% for lamivudine). However, these efficacy differences were not analyzed statistically because of the limited power for statistical comparisons within the small HBeAg-negative patient population. No patient experienced HBsAg loss or seroconversion. Both study drugs were generally well tolerated. Adverse events were reported in about half of the patients in both treatment arms; most adverse events were not attributed to the study drug by the clinical investigators.
Liaw et al.[71] (2009) Telbivudine 600 mg	RCT, DB, MC Adults aged 16–70 years with HBeAg-positive or	N=1,370 2 years	Primary: Therapeutic response (defined as reduction of serum HBV DNA	Primary: In HbeAg-positive and HBeAg-negative patients at week 104, therapeutic response was achieved by significantly more recipients of telbivudine (63.3% and 77.5%, respectively) than lamivudine (48.2% and 66.1%, respectively; P<0.001 and P<0.007).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
once daily vs lamivudine 100 mg once daily	HBeAg-negative chronic hepatitis B and compensated liver disease		levels to <5 log_{10} copies/mL and normalization of ALT level or loss of serum HbeAg) Secondary: Serum HBV DNA changes from baseline, proportion of patients with HBV DNA non-detectable (<300 copies/mL), HbeAg loss and seroconversion, normalization of serum ALT level	Secondary: Reductions in serum HBV DNA level from baseline to week 104 were significantly greater with telbivudine compared with lamivudine in HBeAg-positive and HbeAg-negative patients. At week 104, serum HBV DNA was non-detectable in significantly more patients treated with telbivudine versus lamivudine in HBeAg-positive patients and HBeAg-negative patients. The mean time required to achieve non-detectable HBV DNA was significantly shorter with telbivudine versus lamivudine in HBeAg-positive patients (34 vs 39 weeks; P<0.001) and also in HBeAg-negative patients (20 vs 26 weeks; P<0.001). The rates of serum ALT normalization at week 104 were 70% and 62% among HBeAg-positive patients treated with telbivudine and lamivudine, respectively (P <0.05). In HBeAg-negative patients, normalization of ALT level by week 104 was achieved by 78% and 70% of telbivudine and lamivudine recipients, respectively (P=0.073). In all HBeAg-positive patients, a larger proportion of telbivudine recipients experienced HBeAg loss compared with lamivudine (P=0.056). The rates of HBeAg loss and seroconversion were proportionally greater in telbivudine compared with lamivudine recipients at all study visits from week 12 to week 104 and the difference increased over time. The proportion of patients reporting at least one adverse event through week 104 was similar for telbivudine and lamivudine (81% vs 77%, respectively).
Woo et al.[97] (2010) Lamivudine, adefovir, entecavir, peginterferon,	MA Adults with HBeAg-positive and/or HBeAg-negative HBV	20 trials 12 months	Primary: HBV-DNA levels <1000 copies/mL normalization of ALT levels HBeAg loss with seroconversion	Primary: <u>Adefovir (4 trials)</u> HBeAg (+) Patients and HBeAg (-) Patients: Adefovir was not significantly better than lamivudine for outcomes. Adefovir did not rank in the top 4 for any outcome.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
telbivudine, tenofovir			decreased HBsAg titer improved liver histology, adverse events	Entecavir (3 trials) HBeAg (+) Patients: Entecavir demonstrated greater efficacy compared to lamivudine in liver histology improvement (OR 1.56, 95% CI, 1.12-2.19). Entecavir ranked first in predicted probability of improving liver histology (PP 0.56, 95% CI, 0.12-0.94). Entecavir ranked in the top 5 therapies for all other outcomes. HBeAg (-) Patients: In direct comparisons, entecavir was not more efficacious than lamivudine. In indirect comparisons, entecavir was more efficacious than lamivudine for all outcomes and ranked in the top 4 for all outcomes. Lamivudine (10 trials) HBeAg (+) Patients: In direct comparisons, placebo was significantly less effective than lamivudine at ALT normalization (OR 0.11, 95% CI, 0.03-0.38) and improving liver histology (OR 0.27, 95% CI, 0.09-0.84). In indirect comparisons, lamivudine was superior to placebo in all outcomes except HBsAg loss. HBeAg (-) Patients: Lamivudine was more effective than placebo in indirect comparisons at achieving undetectable HBV-DNA. Lamivudine was ranked in the bottom 2 therapies for all other outcomes. Peginterferon (2 trials) HBeAg (+) Patients: In direct comparisons, PEG-INF was more effective than lamivudine monotherapy for HBeAg loss and HBsAg loss.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				PEG-INF was within the top 4 therapies for HBeAg seroconversion, HBeAg loss, HBsAb loss, and histologic improvement of the liver. HBeAg (-) Patients: PEG-INF was less effective than lamivudine in achieving undetectable HBV-DNA or ALT normalization. <u>Telbivudine (4 studies)</u> HBeAg (+) Patients: In direct comparisons, telbivudine was more effective at achieving undetectable HBV-DNA compared to lamivudine (OR, 2.34, 95% CI, 1.31-5.36) and liver histology improvement (OR 1.41, 95% CI, 1.09-1.84). Telbivudine ranked second for HBeAg loss and ranked last for HBsAg loss. HBeAg (-) Patients: In direct comparisons, telbivudine was not more efficacious than lamivudine. <u>Tenofovir (1 study)</u> HBeAg (+) Patients: In indirect comparisons, tenofovir showed greater efficacy compared to lamivudine at achieving undetectable HBV-DNA (OR 23.34, 95% CI, 6.19-76.39). Tenofovir ranked in the top 3 for all outcomes except HBeAg loss (no data). Tenofovir ranked first for achieving undetectable HBV-DNA (PP: 0.88, 95% CI, 069-0.97); normalization of ALT levels (PP: 0.66, 95% CI, 0.41-0.91); HBeAg seroconversion (PP: 0.2, 95%CI 0.07-0.43); HBsAg loss (PP: 0.05, 95% CI, 0-0.54). HBeAg (-) Patients: In direct comparisons, tenofovir was not more efficacious than lamivudine. In indirect comparisons, tenofovir ranked first for HBV-DNA suppression,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				histologic improvement and second for ALT normalization. <u>Lamivudine + Peginterferon</u> HBeAg (+) Patients: In direct comparisons, combination therapy was more effective than lamivudine monotherapy at inducing undetectable HBV-DNA (OR: 3.08, 95% CI, 1.88-4.91). The combination was ranked first in inducing HBeAg loss (PP: 0.39, 95% CI, 0.18-0.63); ranked third for HBeAg seroconversion; ranked second for HBsAg loss. HBeAg (-) Patients: Combination therapy was more effective than lamivudine at inducing undetectable HBV-DNA levels (OR 2.40, 95% CI, 1.41-4.19). Combination therapy was less effective than lamivudine at inducing normalization of ALT levels (OR: 0.35, 95% CI, 0.23-0.55). <u>Lamivudine + Telbivudine</u> HBeAg (+) Patients: There was no benefit with combination therapy over lamivudine monotherapy. <u>Lamivudine + Adefovir</u> HBeAg (+) Patients: There was no benefit with combination therapy over lamivudine monotherapy.
Hepatitis C				
Brok et al.[61] (2005) Interferon monotherapy vs	MA Patients with hepatitis C patients without HIV who received interferon monotherapy or a combination of	N=9,991 (72 trials) Variable duration	Primary: Failure of sustained virologic response (SVR) ≥6 months and liver-related morbidity plus all-cause mortality	Primary: Compared to monotherapy, combination therapy with ribavirin significantly reduced the number with failure of SVR (RR 0.73; 95% CI, 0.71 to 0.75). For the combined total of all patients studied, combination therapy significantly reduced morbidity and mortality (OR 0.46, 95% CI: 0.22 to 0.96); however, morbidity and mortality were not significantly reduced

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
interferon in combination with ribavirin	ribavirin and interferon		Secondary: Failure of end-of-treatment virologic response, failure of histological response, quality of life (QOL) and adverse events	compared to patients classified as naïve alone, nonresponders alone, or relapsers alone. Secondary: Combination therapy significantly reduced the number of patients with failure of virologic response at end-of-treatment (RR=0.70, 95% CI: 0.67 to 0.72). Failure of histological response was significantly reduced with combination therapy, significantly reducing the number of patients with failure with grading (RR=0.84, 95% CI: 0.80 to 0.87) and staging (RR=0.95, 95% CI: 0.92 to 0.97). Where measured, combination therapy was found to significantly increase QOL, including measures of general health, social functioning and mental health. Anemia was reported in 22% of patients on combination therapy compared to 0.8% on monotherapy therapy (RR=18.22, 95% CI: 12.92 to 25.70). Rates of leukopenia were significantly higher in patients treated with combination therapy (RR=4.32, 95% CI: 1.56 to 11.90). Rates of dermatological and gastrointestinal adverse events also occurred significantly more often with combination therapy.
Chung et al.[66] (2004) Interferon alfa-2a 6 MIU TIW for 12 weeks, then 3 MIU for 36 weeks plus ribavirin vs peginterferon alfa-2a 180 mcg/week for 48	RCT Adult HIV-infected patients with a confirmed diagnosis of hepatitis C not previously treated with interferon alfa	N=133 48 weeks	Primary: Virologic response at 24 weeks Secondary: Sustained virologic response (SVR) 24 weeks after treatment, virologic response at end of treatment, histologic response and changes in HIV control	Primary: At 24 weeks, 44% of patients on peginterferon had a virologic response compared to 15% on interferon (P<0.001). Secondary: SVR 24 weeks after treatment was reported in 27% of patients on peginterferon compared to 12% on interferon (P<0.03). At the end of treatment, 41% of patients on peginterferon had a virologic response compared to 12% on interferon (P<0.001). In patients without a virologic response, histologic response was reported in 35% of patients on peginterferon and 36% on interferon.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks plus ribavirin				CD4 cell counts increased 3.5% in patients on peginterferon and 3.0% on interferon. Rates of influenza-like symptoms, depression, and decreases in hemoglobin occurred at comparable rates between treatment groups. Eight patients in each treatment group were withdrawn due to an adverse event or laboratory value abnormality.
Nevens et al.[94] (2010) Interferon alfa-2a 6 MIU TIW for 8 weeks, then 3 MIU TIW plus ribavirin vs peginterferon alfa-2a 180 mcg/week plus ribavirin	MC, OL, RCT Adult patients with chronic hepatitis C	N=443 24-48 weeks	Primary: Sustained virologic response (SVR) rate as assessed by PCR 24 weeks after treatment Secondary: Sustained biochemical response rate (abnormal ALT) at 24 weeks after treatment; proportion of patients with undetectable HCV RNA at weeks 12, 24, and 48	Primary: After 24 weeks, SVR rates were significantly greater in the peginterferon group compared to the interferon group (52% vs 27%, P<0.001). Secondary: Sustained biochemical response rates were significantly greater in the peginterferon group compared to the interferon group (53% vs 34%, P<0.001). In respect to undetectable HCV RNA levels at weeks 12, 24, and 48, the peginterferon group had rates of 70%, 84%, and 87%, while the interferon group had rates of 42%, 52%, and 73%, respectively. A total of 190 patients (42.8%) discontinued therapy prematurely due to a lack of efficacy, adverse events, personal reasons, and lack of follow-up data. In the patients who did continue therapy, hematologic abnormalities were the most common adverse events with rates of anemia (29.7% vs 19.8%), thrombocytopenia (23.1% vs <10%), leucopenia (21.8% vs 10.4%) and neutropenia (18.3% vs <10%) for the peginterferon group compared to the interferon group.
McHutchison et al.[62] (1998) Interferon alfa-2b 3 MIU TIW for 24-48 weeks vs	DB, PC, RCT Adult patients with hepatitis C	N=912 24-48 weeks	Primary: Sustained virologic response (SVR) 24 weeks after treatment Secondary: ALT and histologic improvement	Primary: SVR was significantly higher for all those on combination therapy (31% to 38%) compared to those receiving interferon alone (6% to 13%; P<0.001). Secondary: ALT levels normalized at the end of treatment in 58% to 65% of patients on combination therapy compared to 24% to 28% on monotherapy. Histologic improvement was significantly higher in patients on

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
interferon alfa-2b 3 MIU TIW plus ribavirin 1,000-1,200 mg QD for 24 or 48 weeks				combination therapy (57% to 61%) compared to those on monotherapy (41% to 44%). Anemia necessitating a reduction in ribavirin dose occurred in 8% of patients on combination therapy. Dyspnea, pharyngitis, pruritus, rash, nausea, insomnia, and anorexia were more common with combination therapy than monotherapy. Dose reductions due to an adverse event occurred in 13% to 17% of patients on combination therapy compared to 9% to 12% in monotherapy.
Enriquez et al.[63] (2000) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000-1,200 mg QD for 24 weeks vs interferon alfa-2b 3 MIU TIW plus ribavirin 1,000-1,200 mg QD for 48 weeks	RCT Adult patients with hepatitis C who had previously received one or more courses of interferon alfa without achieving a sustained response	N=120 24-48 weeks	Primary: Virologic response at end of treatment and Sustained virological response (SVR) at 6 months after treatment	Primary: Virologic response at the end of therapy was 44.8% in those treated for 24 weeks and 46.8% in those treated for 48 weeks (P=0.85). SVR at 6 months was significantly higher in those treated for 48 weeks (37.1% vs 15.5%; P=0.013). Dose adjustments due to decreased hemoglobin levels occurred in 5% of patients treated for 48 weeks and 3% in those treated for 24 weeks. Influenza-like symptoms were reported in most patients for both treatment groups during the first 2-4 weeks.
Poynard et al.[65] (1998) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000-1,200 mg QD for 24 weeks vs interferon alfa-2b	MC, PC, RCT, Adult patients with compensated hepatitis C not previously treated	N=832 48 weeks	Primary: Sustained virologic response (SVR) at week 24 after treatment Secondary: ALT and histological improvement	Primary: SVR was significantly higher for both combination regimens compared to monotherapy (P<0.001). SVR was observed in 43% of combination therapy patients treated for 48 weeks and in 35% of those treated for 24 weeks compared to 19% with SVR among those treated with monotherapy. Secondary: ALT normalization was significantly higher with combination therapy patients treated for 48 weeks (50%) compared to those treated for 24 weeks (39%; P=0.02) and those on monotherapy (24%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
3 MIU TIW plus ribavirin 1,000-1,200 mg QD for 48 weeks vs interferon alfa-2b 3 MIU TIW plus placebo for 48 weeks				Inflammation improvement was significantly higher in patients on 48 weeks of combination therapy (63%) compared to those on 24 weeks therapy (52%; P=0.05) and monotherapy (39%; P<0.001). Those on 24 weeks of combination therapy had significantly greater improvement in inflammation compared to monotherapy (52% vs 39%; P=0.007). Significantly more patients treated for 48 weeks (monotherapy and combination therapy) discontinued therapy due to an adverse reaction, compared to those treated for 24 weeks.
Sjogren et al.[64] (2005) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000 mg day vs interferon alfacon-1 15 mcg TIW plus ribavirin 1,000 mg/day	RCT Adult patients with chronic hepatitis C	N=128 48 weeks	Primary: Sustained virologic response (SVR) at 24 weeks after treatment Secondary: Virologic response based on baseline viral load and response of those with genotype 1	Primary: Twenty-four weeks after treatment, 57% of patients on interferon alfacon-1 had SVR compared to 40% on interferon alfa-2b (P=0.052). Secondary: In patients with a high viral load, a virologic response was observed in 57% of patients on interferon alfacon-1 compared to 31% on interferon alfa-2b (P=0.025). In patients with genotype 1, a response was observed in 46% of patients on interferon alfacon-1 compared to 14% on interferon alfa-2b (P=0.019). Drug-related adverse events were comparable between treatment groups.
Manns et al.[67] (2001) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000-1,200 mg daily vs peginterferon alfa-2a 1.5	RCT Adult patients with a confirmed diagnosis of hepatitis C not previously treated	N=1,530 48 weeks	Primary: Sustained virologic response (SVR) Secondary: SVR for genotype 1, 2, and 3	Primary: SVR rates were significantly higher for the high-dose peginterferon regimen (54%) compared to low-dose peginterferon (47%; P=0.01) and interferon (47%; P=0.01). Secondary: The SVR rate for genotype 1 was 42% for the high-dose peginterferon regimen compared to 34% for low-dose peginterferon and 33% for interferon (P=0.02 vs high-dose peginterferon). The SVR rates for genotype 2 and 3 were approximately 80% for all treatment groups. The side-effect profiles were comparable among treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mcg/kg/week plus ribavirin 800 mg daily vs peginterferon alfa-2a 1.5 mcg/kg/week for 4 weeks, then 0.5 mcg/kg/week plus ribavirin 1,000-1,200 mg daily				
Carrat et al.[68] (2004) Interferon alfa-2b 3 MIU TIW plus ribavirin 800 mg daily for 48 weeks vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800 mg daily for 48 weeks	RCT Adult HIV-infected patients with a confirmed diagnosis of hepatitis C not previously treated with interferon alfa	N=412 72 weeks	Primary: Sustained virologic response (SVR) at week 72 Secondary: Histological improvement, as measured by Metavir score and Ishak grade	Primary: SVR rates were significantly higher for the peginterferon regimen (27%) compared to interferon (20%; P=0.01). Secondary: Metavir scores decreased significantly with the peginterferon regimen (-0.19) compared to interferon (0.01; P=0.02). Mean changes in Ishak score were –0.57 for peginterferon and –0.26 with interferon (P=0.24). Doses of peginterferon were modified in 16% of patients due to clinical adverse events compared to 7% with interferon (P=0.004). Dose adjustments due to laboratory abnormalities occurred in 20% of patients on peginterferon and 7% with interferon (P=0.004). Treatment discontinuation due to an adverse event was comparable between treatment groups.
Fried et al.[69] (2002) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000-1,200 mg daily vs	RCT Adult patients with a confirmed diagnosis of hepatitis C not previously treated with interferon alfa	N=1,121 48 weeks	Primary: Sustained virologic response (SVR) at 24 weeks after therapy Secondary: Virologic response at end of therapy	Primary: SVR rates 24 weeks after therapy were significantly higher for the peginterferon combination regimen (56%) compared to the interferon combination regimen (44%; P<0.001) and peginterferon monotherapy regimen (29% P<0.001). Secondary: Virologic response rates at end of therapy were significantly higher for the peginterferon combination regimen (69%) compared to interferon (52%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
peginterferon alfa-2a 180 mcg/week vs peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg/day			and virologic response for genotype 1, 2, and 3	P<0.001) and peginterferon monotherapy (59% P=0.01). SVR rates for genotype 1 were significantly higher for the peginterferon combination regimen (46%) compared to interferon (36%; P=0.01) and peginterferon monotherapy (21%; P<0.001). SVR rates for genotype 2 or 3 were significantly higher for the peginterferon combination regimen (76%) compared to interferon (61%; P=0.005) and peginterferon monotherapy (45%). Withdrawals due to adverse events were comparable between treatment groups. The most common reason for discontinuation was a psychiatric disorder. Both peginterferon regimens had a lower incidence of influenza-like symptoms and depression compared to interferon (P<0.05).
Lam et al.[110] (2010) Peginterferon alfa-2a 180 mcg/week plus ribavirin 800-1,200 mg daily for 24 weeks vs peginterferon alfa-2a 180 mcg/week plus ribavirin 800-1,200 mg daily for 48 weeks	OL, MC, RCT Treatment-naïve adults with chronic hepatitis C genotype 6	N=60 24 to 48 weeks	Primary: Sustained virological response (SVR) at the end of treatment period Secondary: Rapid virologic response (RVR), complete early virologic response (EVR), end of treatment response(ETR), biochemical response, and treatment adherence	Primary: At the end of the treatment period, there was no significant difference between the patients randomized to either 24 or 48 weeks of peginterferon for sustained virologic response (70% for 24 weeks vs 79% for 48 weeks, P=0.48). Secondary: Of the subgroup of patients who had HCV RNA PCR testing at week 4 of therapy, 85% in the 24 week group and 63% in the 48 week group achieved RVR (P=0.12). RVR was a significant predictor of SVR in the 48-week group and trending towards significance in the 24-week group: 82% and 83% of those with RVR achieved SVR compared to 33% and 29% for the 24-week and 48-week groups, respectively (P=0.07 and P=0.02). A similar percentage of patients in both the 24-week and 48-week groups achieved complete EVR (96% versus 97%, P=0.90) and ETR (89% versus 94%, P=0.48). Normalization of serum ALT levels 6 months after therapy was lower in the 24-week group compared to the 48-week group (78% versus 91%; P=0.16).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Treatment adherence was 63% in the 24-week group compared to 79% for the 48-week group (P=0.18). There were no differences between the two treatment groups for rates of adverse events.
Ferenci et al.[120] (2010) Peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg/day for 48 weeks (group A) vs peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg/day for 72 weeks (group B)	RCT, MC Adult patients with chronic hepatitis C genotype 1/4 who had early virologic response (undetectable HCV RNA at 24 weeks)	N=517 24 weeks posttreatment	Primary: Relapse and sustained virologic response (SVR; defined as an undetectable HCV RNA at the end of the 24 week follow-up)	Primary: The relapse rate was 33.6% in group A and 18.5% in group B (P=0.0115). The SVR rate was 51.1% in group A and 58.6% in group B (P>0.1). The overall SVR rate was 50.4%, including 115 of 150 patients with an RVR treated for 24 weeks and 4 of 78 patients without an EVR. There was no significant difference for rates of adverse events between the two treatment groups. Overall, there was a 17.3% adverse event rate in the 48 week group and 22.7% adverse event rate in the 72 week group.
Di Bisceglie et al.[119] (2007) Peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg/day for 12 weeks	OL, RCT Treatment-naïve adult patients with chronic hepatitis C genotype 1	N=341 12 weeks	Primary: Change in HCV-RNA concentration at week 12 Secondary: Incidence of adverse events	Primary: At the end of week 12, there was no significant difference between the two treatment groups for change in HCV-RNA concentration. There was also no significant difference at weeks 4 and 8. Secondary: There was no significant difference between the two treatment groups for rates of adverse events. However, there was an increase in the relative frequency of chills, fever, influenza-like illness, decreased appetite, rash, vomiting, and injection site reactions in the peginterferon alfa-2b group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 1,000-1,200 mg/day for 12 weeks				
Escudero et al.[118] (2008) Peginterferon alfa-2a 180 mcg/week plus ribavirin 800-1,200 mg/day vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,200 mg/day The duration of treatment was 24 weeks for patients with HCV genotypes 2 or 3, and 48 weeks for those with HCV genotypes 1 or 4.	OL Treatment-naïve adult patients with chronic hepatitis C	N=183 24 weeks posttreatment	Primary: Sustained virological response (SVR; defined by undetectable HCV RNA at week 72) Secondary: Rapid virological response at 4 weeks, early virological response at 12 weeks, transient virological response, adverse events	Primary: There was no significant difference between the two treatment groups for SVR (65.9% for PEG-INF alfa-2a group vs 62% for PEG-INF alfa-2b group, P=0.64). There were no differences in the percentage of patients with sustained virological response according to HCV genotype. In the subset of patients with HCV genotype 1, 50.8% of those treated with PEG-IFN alfa-2a plus ribavirin achieved sustained virological response compared with 46.6% for PEG-IFN alfa-2b plus ribavirin (P=0.713). The corresponding figures for HCV genotype 2/3 were 95% versus 89.3% (P=0.63) and for genotype 4 were 91.7% versus 83.3% (P=1.0). Other efficacy variables including rapid virological response at 4 weeks, early virological response at 12 weeks and transient virological response were also similar among patients in both treatment groups. There were similar rates of adverse events in both treatment groups as well as discontinuation of study drug due to adverse events (22 patients alfa-2a group vs 28 patients alfa-2b group, P=NS).
Scotto et al.[117] (2008) Peginterferon	OL, RCT Adult patients with chronic hepatitis C	N=108 24 weeks posttreatment	Primary: Sustained virological response (SVR;	Primary: At the end of the 72-week period, there was no difference between the two treatment groups for SVR (20.4% for PEG-INF alfa-2a vs 18.5% for PEG-INF alfa-2b, P=NS).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
alfa-2a 180 mcg/week plus ribavirin 15 mg/kg/day for 48 weeks vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 15 mg/kg/day for 48 weeks	who were unresponsive to previous combined therapy (standard interferon alfa plus ribavirin for ≥3 months)		defined by undetectable serum HCV RNA at 72 weeks) Secondary: Sustained biochemical response, adverse events	Secondary: There was no difference in normalization of ALT levels at the end of the 72-week period (22.2% PEG-INF alfa-2a group vs 24.1% PEG-INF alfa-2b group, P=NS). In terms of adverse events, there was no difference between the two groups.
Rumi et al.[116] (2010) Peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg/day for 24-48 weeks (depending on genotype) vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,200 mg/day for 24-48 weeks (depending on genotype)	OL, RCT Treatment-naïve adult patients with chronic hepatitis C	N=431 24 weeks posttreatment	Primary: Sustained virological response (SVR; undetectable HCV-RNA 24 weeks after treatment), adverse events	Primary: The overall SVR rate was higher in PEG-IFN alfa-2a group than in PEG-INF alfa-2b group (66% vs 54%, respectively, P=0.02). In patients with genotype 1 and 4, the SVR rates were 48% and 32% with PEG-IFN alfa-2a and PEG-IFN alfa-2b, respectively (P=0.04). In patients with genotype 2, the SVR rates were 96% and 82% with PEG-IFN alfa-2a and PEG-IFN alfa-2b, respectively (P=0.01). Rates of adverse events were similar between the two treatment groups. Eighteen patients in the peginterferon alfa-2a group compared to 23 in the alfa-2b group discontinued therapy due to adverse events.
Ascione et al.[115] (2010)	RCT, OL	N=320	Primary: Sustained virologic	Primary: SVR was achieved in 68.8% of patients treated with peginterferon alfa-2a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg/day for 48 weeks (genotype 1 or 4) or 24 weeks (genotype 2 or 3) (group A) vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 1,000-1,200 mg/day for 48 weeks (genotype 1 or 4) or 24 weeks (genotype 2 or 3) (group B)	Treatment-naïve adult patients with chronic hepatitis C	24 weeks posttreatment	response (SVR) after 24 weeks of untreated follow-up	compared to 54.4% of patients treated with peginterferon alfa-2b (P=0.008). Higher SVR rates were obtained in group A than group B among patients with genotype 1/4 (54.8% vs 39.8%; P=0.04), with genotype 2/3 (88.1% vs 74.6%; P=0.046), without cirrhosis (75.6% vs 55.9%; P=0.005), and with baseline levels HCV RNA >500,000 IU/mL (69% vs 46.2%; P=0.002). SVR rates in groups A and B were not statistically different among patients with baseline HCV RNA ≤500,000 IU/mL ([68.4% vs 65.7%; P=0.727) or in patients with cirrhosis (42.4% vs 46.1%; P=0.774).
Kamal et al.[114] (2011) Peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000-1,200 mg daily for 48 weeks vs peginterferon	OL, RCT Treatment-naïve adult patients with chronic hepatitis C genotype 4	N=213 24 weeks posttreatment	Primary: Sustained virological response (SVR) defined by undetectable HCV RNA 24 weeks after treatment Secondary: Biochemical response, histological	Primary: Significantly more patients in the PEG-INF alfa-2a group had achieved SVR at the end of the study period compared to the PEG-INF alfa-2b group (70.6% PEG-INF alfa-2a vs 54.6% PEG-INF alfa-2b; P=0.0172). Significantly more patients in the PEG-INF alfa-2b group had relapse compared to the PEG-INF alfa-2a group (15.7% vs 5.1%; P=0.0019). Secondary: Among patients treated with PEG-IFN alfa-2a and ribavirin, 41.3% had undetectable HCV RNA after 4 weeks of therapy (RVR) compared with 27.78% of patients treated with PEG-IFN alfa-2b and ribavirin (P=0.0456).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
alfa-2b 1.5 mcg/kg/week plus ribavirin 1,000-1,200 mg/day for 48 weeks			response, quality of life, adverse events, adherence	Among those who did not achieve RVR, 46.9% and 26.9% of patients in PEG-IFN alfa-2a and PEG-IFN alfa-2b groups, respectively, had undetectable HCV RNA at week 12 (P=0.1213). A total of 39.1% and 30.8% of patients in PEG-IFN alfa-2a and PEG-IFN alfa-2b groups, respectively, had a >2 $\log_{10}$ decline in HCV RNA (P=0.3754). Significantly more patients with RVR went on to achieve an SVR compared with their counterparts who lacked that response (97.3% vs 2.7%; P<0.0001). The mean time duration to aviremia was longer among patients receiving PEG-IFN alfa-2b than PEG-IFN alfa-2a (P=0.0283). Follow-up biopsies, performed on 42 patients showed that the rates of improvement in liver steatosis, liver grading scores and fibrosis scores at the end of the study period did not differ significantly between groups (P>0.05). The SF-36v2 and CLDQ were low during therapy and improved significantly after therapy successful therapy. Overall, there was no significant difference between the two groups for rates of adverse events.
Brixner et al.[113] (2009) Peginterferon alfa-2a plus ribavirin (2a group) vs peginterferon	RETRO Adult patients with chronic hepatitis C	N=1783 Variable duration	Primary: Treatment persistence (duration of prescriptions filled after index date)	Primary: There was no significant difference in persistence rates for patients in the 2a group compared to the 2b group (median time to discontinuation: 245 days vs 226 days, respectively; P=0.072).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
alfa-2b plus ribavirin (2b group)				
Witthoeft et al.[112] (2010) Peginterferon alfa-2a plus ribavirin (group A) vs peginterferon alfa-2b plus ribavirin (group B) Dosing was up to discretion of treating physician.	RETRO Adult patients with chronic hepatitis C	N=3470 24 weeks	Primary: Early virologic response (≥2 $\log^{10}$ drop in HCV RNA or HCV RNA ≤50 IU/mL after 12 weeks), end of treatment response (EOT) and sustained virological response (SVR; HCV RNA ≤50 IU/mL or HCV RNA undetectable after 24 weeks)	Primary: There was no significant difference in any of the virological response parameters measured between group A and group B. Overall, significantly fewer patients in group A discontinued therapy prior to the end of treatment compared to those in group B (21.8% vs 29.6%, P≤0.0001).
Van Vlierberghe et al.[111] (2010) Peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,200 mg/day for 48 weeks	OL, OBS Treatment-naïve adult patients with chronic hepatitis C	N=219 48 weeks	Primary: Sustained virological response (SVR) defined by undetectable HCV RNA 6 months after treatment completion	Primary: A total of 49.3% of patients had an undetectable HCV RNA at the end of 48 weeks of therapy. However, there was a fairly significant dropout rate and loss to follow-up (98 patients; 44.7%). A total of 41 patients discontinued therapy at various time points due to adverse events (n=23) or serious adverse events (n=18). The most common serious adverse events were anemia, fatigue/asthenia/malaise, and fever.
Buti et al.[110] (2010) Peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,400 mg/day for 48	OL, MC, RCT Adult patients with chronic hepatitis C genotype 1	N=1,428 48 to 72 weeks	Primary: Sustained virological response (SVR) at then end of the treatment period Secondary:	Primary: At the end of the treatment period, there was no difference in the rates of SVR between the two treatment groups (43% vs 48%, P=0.644). Secondary: End-of-treatment response was 83% and 70% in groups A and B, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks (group A) vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,400 mg/day for 72 weeks (group B)			End-of-treatment virologic response, relapse rates, adverse events	Relapse rates were similar in slow responders treated for 48 or 72 weeks (47% versus 33%, P=0.169). There was no significant difference between the two groups when comparing adverse events; however the raw rates of adverse events in the group receiving 72 weeks of treatment were higher and may represent a clinical significance (3.5% vs 8.2%).
Brady et al.[109] (2010) Peginterferon alfa-2b 3.0 mcg/kg/week for 12 weeks, then 1.5 mcg/kg/week for 36 weeks, plus ribavirin 11-15 mg/kg/day for 48 weeks (induction group) vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 11-15 mg/kg/day for 48 weeks (SOC)	RCT, OL Treatment-naïve adult patients with chronic hepatitis C genotype 1 or 4	N=610 6 months	Primary: Sustained virologic response (SVR) defined as persistent loss of HCV RNA at 6 months of follow-up evaluation after completion of 48 weeks of treatment = week 72) Secondary: Early virologic response (virus-negative at week 12); subgroup analysis of SVR response in African American and Hispanic populations	Primary: Complete early virologic response was 62.6% versus 57.7% in induction versus SOC (P=NS). Overall SVR was 32% in the induction group versus 29% in SOC group (P=0.434). Secondary: A total of 48.8% of patients from the induction group and 42.8% of patients from the SOC group discontinued therapy before 48 weeks (P=0.2). Overall SVR in African Americans was similar in the patients receiving induction therapy (35%) versus SOC (32%; P=0.9). Overall SVR for Hispanic patients was similar in patients receiving induction therapy (36.1%) versus SOC (22.5%; P=0.292). As shown in other studies with peginterferon alfa-2b combined with ribavirin, there was a large portion of patients experience adverse events. There were no significant life-threatening adverse events reported in any study group. There were also no significant differences between the two study groups for rates of adverse events.
McHutchison et al.[84] (2009)	RCT, DB, MC Patients ≥18 years of age with	N=3,070 24 weeks posttreatment	Primary: Sustained virologic response (defined as undetectable	Primary: The rates of sustained virologic response did not differ significantly among the three treatment groups, with a rate of 39.8% (95% CI, 36.8 to 42.8) for standard-dose peginterferon alfa-2b, 38.0% (95% CI, 35.0 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800 to 1,400 mg/day for 48 weeks (standard-dose arm) vs peginterferon alfa-2b 1.0 mcg/kg/week plus ribavirin 800 to 1,400 mg/day for 48 weeks (low-dose arm) vs peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000 to 1,200 mg/day for 48 weeks	compensated liver disease due to chronic HCV genotype 1 infection and a detectable plasma HCV RNA level who had not been previously treated for hepatitis C infection		HCV RNA levels 24 weeks after the completion of therapy) Secondary: Rates of virologic response during the treatment phase and relapse (defined as an undetectable HCV RNA level at the end of the treatment phase, with a detectable HCV RNA level during the follow-up period)	41.0) for low-dose peginterferon alfa-2b, and 40.9% (95% CI, 37.9 to 43.9%) for peginterferon alfa-2a, (P=0.20 for standard-dose vs low-dose peginterferon alfa-2b; P=0.57 for standard-dose peginterferon alfa-2b vs peginterferon alfa-2a). Secondary: Response rates at the end of the treatment phase were higher with peginterferon alfa-2a than with either peginterferon alfa-2b regimen, however the virologic relapse rate was also higher. HCV RNA suppression at treatment weeks 4 and 12 was strongly associated with achievement of sustained virologic response in all 3 treatment groups. Fewer than 5% of patients who had a reduction from the baseline HCV RNA level of less than 1 $\log_{10}$ IU/ml at week 4 also had a sustained virologic response. A prolonged time (>12 weeks of therapy) to undetectable HCV RNA level was associated with a higher likelihood of relapse after treatment. Rates of sustained virologic response were similar among the three treatment groups, within the subgroups of patients receiving the same dose of ribavirin. Relapse rates were 23.5% for standard-dose peginterferon alfa-2b, 20.0% for low-dose peginterferon alfa-2b, and 31.5% for peginterferon alfa-2a (95% CI, –13.2 to –2.8 for the standard dose regimens; 95% CI, –1.6% to 8.6% for standard-dose peginterferon alfa-2b vs low-dose peginterferon alfa-2b). The types and frequencies of adverse events were similar among the three groups. The most common adverse events included influenza- like symptoms, depression, and the hematologic events of anemia and neutropenia. The proportion of patients with neutropenia was 21.1% in patients receiving peginterferon alfa-2a, 19.4% in patients receiving standard-dose peginterferon alfa-2b, and 12.5% in patients receiving low-dose peginterferon alfa-2b. Most psychiatric adverse events were mild or moderate and were not treatment-limiting.
Herpes Simplex Virus Infections				

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chosidow et al.[55] (2001) Acyclovir 200 mg five times daily for 5 days vs famciclovir 125 mg BID for 5 days	DB, PG, RCT Adult patients with genital herpes who had ≥3 occurrences within the past 12 months	N=204 10 days	Primary: Lesion healing time, defined as re-epithelialization of the lesions Secondary: Proportion of healed lesions at the different days of clinical evaluation and duration of symptoms	Primary: Mean healing times were 5.13 days with famciclovir and 5.38 days with acyclovir (difference 0.25 days, 95% CI:–0.32 to 0.82). Famciclovir was considered statistically equivalent to acyclovir. Secondary: There were no significant differences between the 2 treatment groups in the proportion of patients having complete healing at the different days of evaluation. Duration of symptoms was comparable between treatment groups. Drug-related adverse events did not differ between treatment groups in severity or frequency. The most commonly reported adverse events included headache, nausea, gastrointestinal disorder and sore throat.
Romanowski et al.[56] (2000) Acyclovir 400 mg five times daily for 7 days vs famciclovir 500 mg BID for 7 days	DB, PG, RCT Adult patients with HIV clinically diagnosed with mucocutaneous HSV infection (orolabial or genital) and prior history of lesions	N=293 7 days	Primary: Proportion of patients developing new lesions during treatment Secondary: Time to complete healing, time to cessation of viral shedding, duration of lesion-associated symptoms and number of withdrawals due to treatment failure	Primary: The percentage of patients developing new lesions occurred in 16.7% of the famciclovir-treated patients and 13.3% of the acyclovir-treated patients (95% CI:–4.8 to 11.5). Secondary: Median time to complete healing was calculated as 7 days in both treatment groups (HR 1.01, 95% CI: 0.79 to 1.29, P=0.95). Median time to cessation of viral shedding was 2 days for both treatment groups (HR 0.93, 95% CI: 0.68 to 1.27, P=0.64). Median time to loss of lesion-associated symptoms was 4 days in both treatment groups (HR 0.99, 95% CI: 0.75 to 1.30, P=0.93). Two patients treated with acyclovir and one patient treated with famciclovir withdrew due to treatment failure. The occurrence of drug-related adverse events was comparable between treatment groups. The most commonly reported adverse events were headache, nausea, and diarrhea.
Warkentin et al.[57]	RCT, SB	N=151	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2002) Acyclovir 400 mg TID vs valacyclovir 500 mg BID vs valacyclovir 250 mg BID	Patients ≥16 years old with a hematologic malignancy receiving chemotherapy or undergoing stem cell transplant positive for HSV antibody	Median 35 days	Incidence of HSV infection Secondary: Evidence of CMV infection or disease, VZV infection, and genital or disseminated HSV	The incidence of HSV infection was similar between all treatment groups (P=0.08). Secondary: None of the patients developed CMV infection or disease, VZV infection, or genital or disseminated HSV infection during the study. Overall rates of adverse events were comparable between the 3 treatment groups (P=0.53). Gastrointestinal adverse events were most commonly reported (48%) followed by nephrotoxicity (30%).
Wald et al.[58] (2006) Famciclovir 250 mg BID vs valacyclovir 500 mg QD	DB, RCT (2 trials) Two randomized trials of adult patients with recurrent genital herpes with ≥6 recurrences in the past year	N=390 10-16 weeks	Primary: Time to recurrence, proportion of days with HSV detected by polymerase chain reaction (PCR) Secondary: Time to first virologic-confirmed recurrence and proportion of days with subclinical shedding	Primary: Time to recurrence was comparable between the two treatment groups (HR=1.17, 95% CI: 0.78 to 1.76, P=0.45). HSV was detected by PCR on 3.2% of days with famciclovir compared to 1.3% of the days with valacyclovir (HR=2.33, 95% CI: 1.18 to 4.89, P=0.014). Secondary: Time to virologic-confirmed recurrence was significantly shorter with famciclovir compared to valacyclovir (HR=2.15, 95% CI: 1.00 to 4.60, P=0.049). HSV shedding was detected on 32.4% of days with famciclovir compared to 1.1% of the days with valacyclovir (HR=2.05, 95% CI: 1.07 to 4.11, P=0.031). Drug-related adverse events were mild and comparable between treatment groups. The most commonly reported adverse event was headache.
Abudalu et al.[82] (2008) Famciclovir 1 g	RCT, DB, MC Immunocompetent adults aged ≥18	N=1,179 14 days	Primary: Time to healing (defined as loss of crust plus re-	Primary: In the modified ITT population, the time to healing of non-aborted lesions was similar for patients who received single-day famciclovir (4.25 days) and patients who received 3-day valacyclovir (4.08 days; P=0.48).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
twice daily as a single dose vs valacyclovir 500 mg twice daily for 3 days	years with genital herpes, laboratory evidence of HSV infection, and experienced ≥4 recurrences of genital herpes in the preceding 12 months		epithelialization of all non-aborted lesions) Secondary: Proportion of patients with aborted lesions and patient-reported time to resolution of genital herpes-associated symptoms	In the per protocol population, the time to healing of non-aborted lesions was similar for patients who received single-day famciclovir (4.45 days) and patients who received 3-day valacyclovir (4.14 days; P=0.44). Secondary: A similar proportion of patients in both treatment groups comprising the ITT population experienced aborted lesions, including 32.7% (121 of 370 patients) in the famciclovir group and 33.6% (128 of 381) in the valacyclovir group. In the ITT population, patients receiving single-day famciclovir had similar median times to resolution of all symptoms associated with recurrent genital herpes, as well as similar median time to resolution of each individual symptom (i.e., pain, itching, tingling, burning, and tenderness), compared with the 3-day valacyclovir group.
Bodsworth et al.[75] (2009) Famciclovir 1 g twice daily as a single dose vs valacyclovir 500 mg twice daily for 3 days	RCT, DB, MC Immunocompetent adults aged ≥18 years with genital herpes, laboratory evidence of HSV infection, and experienced ≥4 recurrences of genital herpes in the preceding 12 months	N=751 6 months	Primary: Time to next recurrence, antiviral resistance	Primary: The frequency of patients with next recurrence and the time to next recurrence was similar between those assigned the single-day famciclovir and 3-day valacyclovir regimen. The median time to next recurrence from treatment initiation was 33.5 days in the famciclovir group and 38.0 days in the valacyclovir group. Susceptibility to penciclovir was evaluated in 573 viral isolates obtained before and during treatment of the initial outbreak, or before treatment of the subsequent outbreak. None exhibited resistance to penciclovir.
Lebrun-Vignes et al.[76] (2007) Acyclovir (ACV), famciclovir (FVC), valacyclovir (VACV)	MA Immunocompetent individuals with genital herpes	N=6,158 (14 trials) Variable duration	Primary: Recurrence of genital herpes	Primary: The global RR of developing at least one recurrence during the trial was reduced by 47% (95% CI 45%-49%). The number of patients needed to treat was 2.15 (95% CI 2.06- 2.25). The analysis according to the drug showed the efficacy of each antiviral agent tested (all doses and regimens pooled), with RR reductions of 53% (95% CI 51%-57%) for ACV, 43% (95% CI 41%-47%) for VACV, and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				42% (95% CI 35%-50%) for FCV. Analysis according to the total daily dose of each drug showed that all the studied ACV doses were effective. The best evaluated daily dose was 800 mg. For VACV, all the doses studied were effective with the best evaluated daily dose being 500 mg. The results of this analysis suggested a dose-dependent response with 250 mg/d being less effective than 500 mg/d, and a maximum efficacy above 500 mg/d. For FCV, 125 mg/d was not effective, but higher doses achieved significant efficacy, with a clear dose-effect response between 250 and 750 mg/d. For ACV 800 mg/d, all regimens (once, twice, or 4 times daily) had significant efficacy, with the best evaluated regimen being the twice-daily (400 mg) schedule (total 800 mg). No difference in efficacy was found between the two (once or twice daily) regimens for VACV at 500 mg/d. Only the FCV (250 mg) twice-daily schedule (total 500 mg/d) was effective, with the once-daily administration failing to reach significance.
Herpes Zoster Virus Infections				
Tyring et al.[50] (2001) Acyclovir 800 mg five times daily for 10 days vs famciclovir 500 mg TID for 10 days	DB, MC, RCT Patients 12 years and older with immuno-suppression with clinical evidence of herpes zoster	N=148 10 days	Primary: Proportion of patients with new lesions while on medication, time to complete healing of lesions, and time to resolution of acute phase pain	Primary: New lesion formation was reported in 77% of patients treated with famciclovir and 73% of patients taking acyclovir (95% CI:–9.2 to 18.6%). Median time to complete healing was 20 days with famciclovir and 21 days with acyclovir (HR=0.98, 95% CI: 0.67 to 1.42). Median time to loss of acute phase pain was 14 days with famciclovir and 17 days with acyclovir (HR=1.11, 95% CI: 0.71 to 1.75). Drug-related adverse events reported were comparable between the 2 treatment groups. The most commonly reported adverse events were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				nausea, headache and vomiting.
Shafran et al.[51] (2004) Acyclovir 800 mg five times a day vs famciclovir 750 mg QD vs famciclovir 500 mg BID vs famciclovir 250 mg TID	DB, MC, RCT Adult patients with herpes zoster lesions for <72 hours	N=559 7 days	Primary: Healing rates	Primary: There were no significant differences between any of the treatment groups in respect to healing rates. The frequency of drug-related adverse reactions was comparable between all treatment groups.
Tyring et al.[52] (2001) Acyclovir 800 mg five times daily for 7 days vs famciclovir 500 mg TID for 7 days	DB, MC, RCT (2 trials) Adult patients with herpes zoster infection involving primarily the ophthalmic branch of the trigeminal nerve	N=454 6 months	Primary: Patients that experienced a severe ocular manifestation (e.g., glaucoma, anterior uveitis, iridocyclitis) and nonsevere manifestations (conjunctivitis, punctate epithelial keratopathy, episcleritis)	Primary: After 6 months, one or more ocular manifestations occurred in 58.0% of famciclovir-treated patients compared to 58.2% of acyclovir-treated patients. There was no significant difference between treatment groups. Secondary: The percentage of patients who experienced one or more severe ocular manifestations was 41.2% in famciclovir-treated patients and 39.8% in acyclovir-treated patients (95% CI, 0.72 to 1.56). There were no significant differences between the treatment groups. The percentage of patients who experienced one or more non-severe ocular manifestation was 44.9% in famciclovir-treated patients and 43.4% in acyclovir-treated patients (95% CI, 0.73 to 1.55). There were no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Proportion of severe and non-severe ocular manifestations and loss of visual acuity	significant differences between the treatment groups. The percentage of patients who experienced visual acuity loss was 2.6% in famciclovir-treated patients and 6.3% in acyclovir-treated patients (OR 0.4, 95% CI: 0.15 to 1.08). There were no significant differences between the treatment groups. Drug-related adverse events were comparable between treatment groups. The most commonly reported adverse events were nausea (10%), headache (5%) and vomiting (5%).
Beutner et al.[53] (1995) Acyclovir 800 mg five times daily for 7 days vs valacyclovir 1,000 mg TID for 7 days vs valacyclovir 1,000 mg TID for 14 days	RCT Adult immunocompetent patients ≥50 years old with herpes zoster	N=1,141 6 months	Primary: Time to resolution of zoster-associated pain, time to cessation of new lesion formation and/or lesion area increase and time to ≥50% healed rash Secondary: Time to resolution of zoster-associated abnormal sensations and pain intensity	Primary: Median time to resolution of zoster-associated pain was 38 days with valacyclovir 7-day treatment (P=0.001 vs acyclovir) and 44 days with valacyclovir 14-day treatment (P=0.03 vs acyclovir) compared to 51 days with acyclovir. Time to cessation of new lesion and time to ≥50% healed rash was 5 days in all treatment groups. Secondary: Median time to resolution of zoster-associated abnormal sensations was 45 days with valacyclovir 7-day treatment (HR 1.18, 95% CI: 0.99 to 1.41 vs acyclovir) and 38 days with valacyclovir 14-day treatment (HR 1.27, 95% CI: 1.07-1.52 vs acyclovir) compared to days with acyclovir. Rates of rash healing were comparable between treatment groups (HR 1.01, 95% CI: 0.93 to 1.30, P=0.26). Pain intensity did not differ among the treatment groups. Drug-related adverse events were comparable among treatment groups and mild in severity. The most commonly reported adverse events were headache, nausea, vomiting, diarrhea and constipation.
Tyring et al.[54] (2000) Famciclovir 500	DB, MC, RCT Immunocompetent patients ≥50 years	N=597 24 weeks	Primary: Time to resolution of zoster-associated pain	Primary: Median time to resolution of zoster-associated pain was 42 days with valacyclovir and 49 days with famciclovir (HR 1.02, 95% CI: 0.84 to 1.23, P=0.84).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg TID for 7 days vs valacyclovir 1,000 mg TID for 7 days	old with herpes zoster		Secondary: Time to resolution of zoster-associated abnormal sensations, rash healing and lesion dissemination	Secondary: Median time to resolution of zoster-associated abnormal sensation was 42 days with valacyclovir and 35 days with famciclovir (HR 1.00, 95% CI: 0.82 to 1.21, P=0.98). Rates of rash healing were comparable between treatment groups (HR 1.01, 95% CI: 0.93 to 1.30, P=0.26). No cases of lesion dissemination were reported. Drug-related adverse events were reported in 34% of patients taking valacyclovir and 38% of patients taking famciclovir. The most commonly reported adverse events were headache, nausea and constipation.
Klein et al.[87] (2011) Valacyclovir 1,000 mg BID (VAC) vs placebo	RCT, DB, PC VZV-seropositive patients undergoing autologous or allogeneic hematopoietic stem cell transplantation	N=53 24 months	Primary: Incidence of herpes zoster	Primary: In the ITT analysis, the incidence of VZV was 11% in the VAC group compared to 23% in the placebo arm (P=0.21). In the MITT analysis, the incidence of VZV was 0% in the VAC group compared to 23% in the placebo arm (P=0.025). A total of 17.4% of patients in both VAC and placebo groups had dose reductions due to myelosuppression; 8.7% and 15.4% in the VAC and placebo arm, respectively had dose reductions due to gastrointestinal toxicity; 4.3% and 7.7% in the VAC and placebo arm, respectively had dose reductions due to musculoskeletal adverse events. There were more discontinuations in the placebo group compared to the VAC group due to gastrointestinal toxicity (7.7% vs 4.3%, respectively). There were more discontinuations in the VAC group due to leucopenia compared to placebo (8.7% vs 0%, respectively).

Drug regimen abbreviations: BID=twice daily, IV=intravenous, PO=oral, PRN=as needed, QD=once daily, QID=four times daily
Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=rate ratio, SB=single-blind
Miscellaneous abbreviations: ALT=alanine aminotransferase, CMV=cytomegalovirus, HIV=human immunodeficiency virus, HSV=herpes simplex virus, MIU=million international units, NS=not significant, VZV=varicella-zoster virus

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 18. Relative Cost of the Nucleosides and Nucleotides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Acyclovir	capsule, injection, suspension, tablet	Zovirax®*	$$$-$$$$	$
Adefovir	tablet	Hepsera®	$$$$$	N/A
Cidofovir	injection	Vistide®	$$$$$	N/A
Entecavir	solution, tablet	Baraclude®	$$$$$	N/A
Famciclovir	tablet	Famvir®*	$$$$$	$$$-$$$$
Ganciclovir	injection	Cytovene®*	$$$$$	$$$$$
Ribavirin	capsule, inhalation solution, solution, tablet	Copegus®*, Rebetol®*, Virazole®	$$$$$	$$$$-$$$$$
Telbivudine	tablet	Tyzeka®	$$$$$	N/A
Valacyclovir	tablet	Valtrex®*	$$$$-$$$$$	$$$
Valganciclovir	solution, tablet	Valcyte®	$$$$$	N/A

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

X. Conclusions

The nucleosides and nucleotides are approved for the treatment of infections caused by herpes simplex virus (HSV), varicella-zoster virus (VZV) and cytomegalovirus (CMV), as well as for the treatment of chronic hepatitis B, chronic hepatitis C, and respiratory syncytial virus.[1-14] Acyclovir, famciclovir, ganciclovir, ribavirin, and valacyclovir are available in a generic formulation.

Cidofovir, ganciclovir and valganciclovir are approved for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS). Studies have demonstrated similar efficacy in terms of protecting vision and guidelines do not give preference to one antiviral agent over another.[32,47-48] Ganciclovir and valganciclovir are also approved for the prevention of CMV disease in transplant patients, and studies have demonstrated similar efficacy with these agents.[46,80-81,83,89,98]

Adefovir, entecavir and telbivudine are approved for the treatment of chronic hepatitis B. Other FDA-approved agents include interferon alfa, peginterferon alfa, lamivudine and tenofovir. Although any of the agents can be used, guidelines recommend peginterferon alfa, tenofovir or entecavir for the initial treatment of patients with HBeAg-positive and HBeAg-negative chronic hepatitis B.[34] Several clinical trials have demonstrated greater efficacy with entecavir and telbivudine than lamivudine.[59-60,71-73,78,97,101] Serum HBV DNA levels were also reduced to a greater extent with telbivudine (24 weeks) and entecavir (12 weeks) compared to adefovir.[74,77] In one study, telbivudine and entecavir decreased HBV-DNA levels to a similar extent after 24 weeks of therapy.[86] However, telbivudine is associated with a high rate of resistance; therefore, telbivudine monotherapy has a limited role in the treatment of hepatitis B.[34] Among the approved therapies for chronic hepatitis B, lamivudine is associated with the highest rate of resistance, and entecavir and tenofovir are associated with the lowest rates of resistance in drug-naïve patients. Judicious use of these agents is the most effective way to reduce the development of resistance.[34] Patients with minimal disease and those who are unlikely to achieve a sustained response should not be treated with the nucleoside/nucleotide analogues, especially if they are <30 years of age.[34]

Oral ribavirin is approved for the treatment of chronic hepatitis C, and guidelines recommend the combination of peginterferon alfa and ribavirin as initial therapy.[28,32,35-36] Ribavirin inhalation solution is approved for the treatment of hospitalized infants and young children with severe lower respiratory tract infection due to respiratory syncytial virus. The American Academy of Pediatrics does not recommended the routine use of ribavirin inhalation solution; however, it may be considered for use in select patients with potentially life-threatening RSV infections.[33]

Acyclovir, famciclovir and valacyclovir are approved for the treatment of herpes simplex virus infections and varicella-zoster virus infections. Guidelines recommend the use of systemic antiviral therapy for the treatment genital herpes and herpes zoster, and do not give preference to one agent over another.[28-30,32,79,85] There are no published guidelines on the management of labial herpes. Several comparative trials have demonstrated similar efficacy with acyclovir, famciclovir and valacyclovir for the treatment of labial and genital herpes, as well as herpes zoster.[50-52,54-58,75-76,82]

Therefore, all brand nucleosides and nucleotides 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 nucleoside or nucleotide 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of HCV Protease Inhibitors
AHFS Class 081840
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I. Overview

The hepatitis C virus (HCV) is a RNA virus that is transmitted through exposure with infected blood.[6-7] Once infected, HCV causes hepatic inflammation and steatosis.[6] With persistent infections, patients may develop hepatic fibrosis, which can lead to cirrhosis and an increased risk for hepatocellular carcinoma. There are six genotypes of HCV; type 1 genotype is the most prevalent in the U.S.[6] There are differences in response to therapy among the genotypes.[7] Type 1 genotype is associated with a lower response to therapy. Thus, a longer duration of therapy is recommended for patients infected with HCV genotype 1. Peginterferon alfa in combination with ribavirin is the standard of care for the treatment for chronic hepatitis C. These agents are administered for 24 to 48 weeks and induce sustained virologic response (SVR) rates of 40%-50% in patients with HCV genotype 1 and ≥80% in patients with HCV genotypes 2 and 3 infections.[8]

The HCV protease inhibitors are approved for use in combination with peginterferon alfa and ribavirin for the treatment of chronic HCV genotype 1 infection.[1-5] Boceprevir and telaprevir are direct-acting antiviral agents.[4-5] They inhibit the NS3/4A viral protease complex, which is one of four viral enzymes essential for viral replication. Use of the HCV protease inhibitors in combination with peginterferon alfa and ribavirin has led to further improvements in SVR rates in treatment-naïve, as well as treatment-experienced patients. Boceprevir and telaprevir must not be used as monotherapy due to the development of resistance.

The HCV protease inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products available. This is a new AHFS subclass, which has not been reviewed previously.

Table 1. HCV Protease Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Boceprevir	capsule	Victrelis®	none
Telaprevir	tablet	Incivek®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the HCV protease inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the HCV Protease Inhibitors

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases (AASLD): **Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection[8] (2011)**	General Considerations • The optimal therapy for genotype 1, chronic HCV infection is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin. • Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin. Treatment-Naive Patients: • The recommended dose of boceprevir is 800 mg administered with food three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 24-44 weeks preceded by 4 weeks of lead-in treatment with peginterferon alfa and ribavirin alone. • Patients without cirrhosis treated with boceprevir, peginterferon, and ribavirin, preceded by 4 weeks of lead-in peginterferon and ribavirin,

Clinical Guideline	Recommendation(s)
	whose HCV RNA level at weeks 8 and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (4 weeks lead-in with peginterferon and ribavirin followed by 24 weeks of triple therapy). • Treatment with all three drugs (boceprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24. • The recommended dose of telaprevir is 750 mg administered with food (not low-fat) three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12-36 weeks of peginterferon alfa and ribavirin. • Patients without cirrhosis treated with telaprevir, peginterferon, and ribavirin, whose HCV RNA level at weeks 4 and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks. • Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peginterferon and ribavirin should receive therapy for a duration of 48 weeks. • Treatment with all three drugs (telaprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >1,000 IU/mL at treatment weeks 4 or 12 and/or detectable at treatment week 24. <u>Treatment-Experienced Patients</u> • Re-treatment with boceprevir or telaprevir, together with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin. • Re-treatment with telaprevir, together with peginterferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peginterferon alfa and/or weight-based ribavirin. • Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers, may be considered for partial responders, but cannot be recommended for null responders. • Patients re-treated with boceprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. • Patients re-treated with telaprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 1,000 IU at weeks 4 or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. • Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose. • Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (>1 log increase in serum HCV RNA above nadir) is observed. • Patients who fail to have a virological response, who experience virological breakthrough, or who relapse on one protease inhibitor should not be re-treated with the other protease inhibitor.
American Association for the Study of Liver Diseases (AASLD): **Diagnosis, Management, and Treatment**	<u>General Information</u> • The goal of therapy is to prevent complications and death from HCV infection. Treatment responses are defined by a surrogate virological parameter rather than a clinical endpoint. Short-term outcomes can be

Clinical Guideline	Recommendation(s)
of Hepatitis C: Update[9] (2009)	measured biochemically (normalization of serum ALT levels), virologicaly (absence of HCV RNA from serum by a sensitive PCR-based assay), and histologically (point improvement in necroinflammatory score with no worsening in fibrosis score). • Several types of virological responses may occur, labeled according to their timing relative to treatment. The most important is the sustained virological response (SVR), defined as the absence of HCV RNA from serum by a sensitive PCR assay 24 weeks following discontinuation of therapy (virological cure). Undetectable virus at the end of either a 24-week or 48-week course of therapy is referred to as an end-of-treatment response (ETR). An ETR does not accurately predict that an SVR will be achieved, but is necessary for it to occur. • The currently recommended therapy of chronic HCV infection is the combination of a pegylated interferon alfa and ribavirin. • Treatment decisions should be individualized based on the severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions, and the patient's readiness for treatment. <u>Genotype1 and Genotype 4 HCV Infection</u> • Treatment with peginterferon plus ribavirin should be planned for 48 weeks. • Treatment may be discontinued in patients who do not achieve an early virological response (EVR; >2 log reduction in HCV RNA at week 12 of treatment). • Patients who do not achieve a complete EVR (undetectable HCV RNA at week 12 of treatment) should be re-tested at week 24, and if HCV RNA remains positive, treatment should be discontinued. • For patients with genotype 1 infection who have delayed virus clearance (HCV RNA test becomes negative between weeks 12 and 24), consideration should be given to extending therapy to 72 weeks. <u>Genotype 2 or Genotype 3 HCV Infection</u> • Treatment with peginterferon plus ribavirin should be administered for 24 weeks. <u>Retreatment</u> • Retreatment with peginterferon plus ribavirin in patients who did not achieve an SVR after a prior full course of peginterferon plus ribavirin is not recommended, even if a different type of peginterferon is administered. • Retreatment with peginterferon plus ribavirin can be considered for non-responders or relapsers who have previously been treated with non-pegylated interferon with or without ribavirin, or with peginterferon monotherapy, particularly if they have bridging fibrosis or cirrhosis. • Maintenance therapy is not recommended for patients with bridging fibrosis or cirrhosis who have failed a prior course of peginterferon and ribavirin. <u>Treatment of Persons with Normal Serum Aminotransferase Values</u> • Regardless of the serum alanine aminotransferase level, the decision to initiate therapy with pegylated interferon and ribavirin should be individualized based on the severity of liver disease by liver biopsy, the potential for serious side effects, the likelihood of response, and the presence of comorbid conditions. • The treatment regimen for HCV-infected persons with normal aminotransferase levels should be the same as that used for persons with elevated serum aminotransferase levels.

Clinical Guideline	Recommendation(s)
	Treatment of Children • Children aged 2-17 years who are infected with HCV should be considered appropriate candidates for treatment using the same criteria as that used for adults. • Children should be treated with pegylated interferon alfa-2b, 60 mcg/m^2 weekly in combination with ribavirin, 15 mg/kg daily for a duration of 48 weeks. Treatment of HIV-infected Persons • Hepatitis C should be treated in the HIV/HCV co-infected patient in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of morbidity from the adverse effects of therapy. • Initial treatment of hepatitis C in most HIV-infected patients should be peginterferon alfa plus ribavirin for 48 weeks at doses recommended for HCV mono-infected patients. • When possible, patients receiving zidovudine (AZT) and especially didanosine (ddI) should be switched to an equivalent antiretroviral agent before beginning therapy with ribavirin. • HIV-infected patients with decompensated liver disease (CTP Class B or C) should not be treated with peginterferon alfa and ribavirin and may be candidates for liver transplantation.

American Gastroenterological Association (AGA): **Medical Position Statement on the Management of Hepatitis C[10] (2006)**	• Therapy is indicated for previously untreated patients with chronic hepatitis C, circulating HCV RNA, elevated aminotransferase levels, evidence on liver biopsy of moderate to severe hepatitis grade and stage, and compensated liver disease.
	• Patients with normal ALT activity are candidates for antiviral therapy or for monitoring without intervention, as determined on an individual basis and as influenced by patient factors such as motivation, genotype, histologic activity, and fibrosis.
	• Patients with compensated cirrhosis who can tolerate therapy are candidates for treatment.
	• The treatment of choice is pegylated interferon alfa plus ribavirin.
	• Patients with genotypes 1 and 4 require 48 weeks of therapy with pegylated interferon and high daily doses of ribavirin (1,000–1,200 mg, depending on weight).
	• Patients with genotypes 2 and 3 can be treated for only 24 weeks with pegylated interferon and with 800 mg of ribavirin daily, with the following exceptions:
	  o A longer duration of therapy may be considered on an individual patient basis taking into account factors such as elevated viral level, cirrhosis, or delayed response to therapy.
	  o 12 weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week 4.
	  o Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks.
	• Therapy with peginterferon alfa and ribavirin should be strongly considered for patients who experienced a relapse after a course of standard interferon alfa/ribavirin combination therapy, while a longer duration of therapy in patients who experienced a relapse after 12 months of treatment with peginterferon alfa plus ribavirin is of unproven efficacy.
	• For children, the general principles of management are the same as those for adults, except that treatment is not recommended for children younger than 3 years.

Clinical Guideline	Recommendation(s)
	• For HIV-infected individuals, the optimal therapy consists of peginterferon alfa plus ribavirin for 48 weeks, regardless of genotype. Because of potential drug-drug interactions in patients on HIV treatment regimens that include didanosine, HIV regimens should be altered in those starting combination therapy for HCV infection. If didanosine is critical to the HIV regimen, ribavirin should be avoided.

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[11] (2008)**	Treatment of Hepatitis C Coinfection
	• Antiviral treatment for HCV infection should be considered for all HIV-infected persons with acute or chronic HCV infection. In the absence of contraindications to peginterferon and/or ribavirin, treatment for HCV infection should be routinely offered to persons in whom the potential benefits of therapy are judged to outweigh the potential risks, including (but not limited to) persons with:
	  o HCV genotype 2 or 3 infection
	  o HCV genotype 1 infection with a low HCV RNA level
	  o Significant hepatic fibrosis (bridging fibrosis or cirrhosis)
	  o Stable HIV infection not requiring ART
	  o Acute HCV infection (<6 months duration)
	  o Cryoglobulinemic vasculitis
	  o Cryoglobulinemic membranoproliferative glomerulonephritis
	  o Strong motivation to treat their HCV infection
	• On the basis of well-designed, randomized, controlled trials, peginterferon plus ribavirin is the recommended treatment for hepatitis C in HIV-infected persons.
	• For all HCV genotypes, the recommended treatment regimen includes either peginterferon alfa-2a or peginterferon alfa-2b plus oral ribavirin for a total duration of 48 weeks.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the HCV protease inhibitors are noted in Table 3. 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 3. FDA-Approved Indications for the HCV Protease Inhibitors[1-5]

Indication	Boceprevir	Telaprevir
Hepatitis C		
Treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy	✔ *	
Treatment of chronic hepatitis C genotype 1 infection in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers		✔

*Boceprevir in combination with peginterferon alfa and ribavirin has not been studied in patients documented to be historical null responders (<2-$\log_{10}$ HCV-RNA decline by treatment week 12) during prior therapy with peginterferon alfa and ribavirin.

IV. Pharmacokinetics

The pharmacokinetic parameters of the HCV protease inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the HCV Protease Inhibitors[1-5]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Boceprevir	Not reported	75	Liver	Renal (9) Feces (79)	3.4
Telaprevir	Not reported	59-76	Liver	Renal (1) Feces (82)	9-11

V. Drug Interactions

Significant drug interactions with the HCV protease inhibitors are listed in Table 5.

Table 5. Significant Drug Interactions with the HCV Protease Inhibitors[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Protease inhibitors (boceprevir, telaprevir)	1	Benzodiazepines	Potentially serious CNS depression is possible when benzodiazepines and protease inhibitors are coadministered.
Protease inhibitors (boceprevir, telaprevir)	1	Cisapride	Cardiac, hematologic, neurologic (seizures), or other potentially serious toxicities are listed in the manufacturer's package labeling when cisapride and protease inhibitors are coadministered.
Protease inhibitors (boceprevir, telaprevir)	1	Colchicine	Plasma concentrations of colchicine may be increased by protease inhibitors. Life-threatening and fatal colchicine toxicity may occur.
Protease inhibitors (boceprevir, telaprevir)	1	Crizotinib	Plasma concentrations and toxic effects of crizotinib may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	1	Direct factor Xa inhibitors	Plasma concentration and pharmacologic effects of direct factor Xa inhibitors may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	1	Docetaxel	Plasma concentrations and pharmacologic effects of docetaxel may be increased by protease inhibitors. Use of boceprevir with docetaxel may increase the risk and/or severity of docetaxel-related toxicity.
Protease inhibitors (boceprevir, telaprevir)	1	Dronedarone	Plasma concentrations and pharmacologic effects of dronedarone may be increased by protease inhibitors.

Generic Name(s)	Significance Level	Interaction	Mechanism
Protease inhibitors (boceprevir, telaprevir)	1	Ergot alkaloids	Pharmacologic effects of ergot alkaloids may be increased by protease inhibitors. Elevated plasma concentrations with toxicity characterized by ergotism may occur.
Protease inhibitors (boceprevir, telaprevir)	1	Fentanyl and related products	Pharmacologic effects and plasma concentrations of fentanyl and related products may be increased by protease inhibitors. Severe respiratory depression may occur.
Protease inhibitors (boceprevir, telaprevir)	1	Immunosuppressive agents	Plasma concentration and pharmacologic effects of Immunosuppressive Agents may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	1	Lurasidone	Plasma concentrations and pharmacologic effects of lurasidone may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	1	Nilotinib	Plasma concentrations and pharmacologic effects of nilotinib may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	1	Phosphodiesterase type 5 inhibitors	Pharmacologic effects of phosphodiesterase type 5 inhibitors may be increased by protease inhibitors. Elevated plasma concentrations with toxicity characterized by hypotension, visual disturbances, and priapism may occur.
Protease inhibitors (boceprevir, telaprevir)	1	Pimozide	Pharmacologic effects of pimozide may be increased by protease inhibitors. Elevated plasma concentrations with cardiovascular toxicity may occur.
Protease inhibitors (boceprevir, telaprevir)	1	Ranolazine	Plasma concentrations and pharmacologic effects of ranolazine may be increased by co-administration of protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	1	Salmeterol	Pharmacologic effects of salmeterol may be increased by protease inhibitors. Elevated salmeterol plasma concentrations with cardiovascular toxicity, such as QT prolongation, palpitations, and tachycardia may occur.
Protease inhibitors (boceprevir, telaprevir)	1	Statins	Plasma concentrations and toxic effects of statins may be increased by protease inhibitors. The risk of myopathy and rhabdomyolysis may be increased.

Generic Name(s)	Significance Level	Interaction	Mechanism
Protease inhibitors (boceprevir, telaprevir)	1	Strong CYP3A4 inducers	Plasma concentrations and pharmacologic effects of protease inhibitors may be decreased by strong CYP3A4 inducers.
Protease inhibitors (boceprevir, telaprevir)	1	Systemic hormonal contraceptives	Plasma concentrations and pharmacologic effects of systemic hormonal contraceptives may be decreased by protease inhibitors. Pregnancy may occur.
Protease inhibitors (boceprevir, telaprevir)	1	Ticagrelor	Plasma concentrations and pharmacologic effects of ticagrelor may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	1	Toremifene	Plasma concentrations and pharmacologic effects of toremifene may be increased by protease inhibitors. Toxicity, including QT prolongation may occur.
Protease inhibitors (boceprevir, telaprevir)	1	Vasopressin receptor antagonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be increased by protease inhibitors.
Telaprevir	1	Digoxin	Plasma concentrations and pharmacologic effects of digoxin may be increased by telaprevir. Signs and symptoms of classic toxicity to digoxin may occur.
Telaprevir	1	HIV protease inhibitors	Plasma concentrations and pharmacologic effects of HIV protease inhibitors may be decreased by telaprevir. Additionally, plasma concentrations and pharmacologic effects of telaprevir may be reduced by HIV protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Brentuximab	Plasma concentrations and pharmacologic effects of brentuximab may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Cabazitaxel	Plasma concentrations and pharmacologic effects cabazitaxel may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Cilostazol	Plasma concentration and pharmacologic effects of cilostazol may be increased by protease inhibitors.

Generic Name(s)	Significance Level	Interaction	Mechanism
Protease inhibitors (boceprevir, telaprevir)	2	Histone deacetylase inhibitors	Plasma concentrations and pharmacologic effects of histone deacetylase inhibitors may be increased by protease inhibitors. The potential for histone deacetylase inhibitors-related adverse effects, including QT prolongation, should be considered.
Protease inhibitors (boceprevir, telaprevir)	2	Imidazoles	Plasma concentrations and pharmacologic effects of protease inhibitors may be increased by imidazoles. In addition, plasma concentrations and pharmacologic effects of imidazoles may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Muscarinic receptor antagonists	Plasma concentrations and pharmacologic effects of muscarinic receptor antagonists may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Oxycodone	Plasma concentrations and pharmacologic effects of oxycodone may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Quinazolines	Plasma concentrations and pharmacologic or toxic effects of quinazolines may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Ruxolitinib	Plasma concentrations and pharmacologic effects of ruxolitinib may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Saxagliptin	Plasma concentrations and pharmacologic effects of saxagliptin may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Tyrosine kinase receptor inhibitors	Plasma concentrations and pharmacologic effects of tyrosine kinase receptor inhibitors may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Vilazodone	Plasma concentrations and pharmacologic effects of vilazodone may be increased by protease inhibitors.
Telaprevir	2	Dihydropyridine calcium channel blockers	Pharmacologic effects of dihydropyridine calcium channel blockers may be increased by telaprevir.
Telaprevir	2	Methadone	Pharmacologic effects and plasma concentrations of methadone may be decreased by telaprevir.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the HCV protease inhibitors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the HCV Protease Inhibitors[1-5]

Adverse Events	Boceprevir	Telaprevir
Central Nervous System		
Asthenia	15	-
Chills	33-34	-
Dizziness	16-19	-
Fatigue	55-58	56
Headache	>10	-
Insomnia	30-34	-
Irritability	21-22	-
Dermatologic		
Alopecia	22-27	-
Dry skin	18-22	-
Pruritus	-	47
Rash	16-17	56
Gastrointestinal		
Abnormal taste	35-44	10
Anal pruritus	-	6
Anorectal discomfort	-	11
Appetite decreased	25-26	-
Diarrhea	24-25	26
Hemorrhoids	-	12
Nausea	43-46	39
Vomiting	15-20	13
Xerostomia	11-15	-
Hematologic		
Anemia	45-50	36
Lymphopenia	-	15
Neutropenia	14-31	-
Thrombocytopenia	1-10	3
Musculoskeletal		
Arthralgia	19-23	-
Weakness	15-21	-
Other		
Dyspnea	8-11	-
Hyperbilirubinemia	-	4-37
Hyperuricemia	-	7-66
Thromboembolic events	<1	-

✓ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the HCV protease inhibitors are listed in Table 7.

Table 7. Usual Dosing Regimens for the HCV Protease Inhibitors[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Boceprevir	Chronic Hepatitis C Genotype 1 Infection: 800 mg 3 times daily in combination with peginterferon alfa and ribavirin Refer to the package insert for information on duration of therapy using response-guided therapy guidelines.	Safety and efficacy in children have not been established.	Capsule: 200 mg
Telaprevir	Chronic Hepatitis C Genotype 1 Infection: 750 mg 3 times daily for 12 weeks in combination with peginterferon alfa and ribavirin	Safety and efficacy in children have not been established.	Tablet: 375 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the HCV protease inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials with the HCV Protease Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kwo et al.[12] (2010) SPRINT-1 Peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,400 mg/day for 48 weeks (PR48) vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,400 mg/day for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 24 weeks (PRB24) vs peginterferon alfa-2b 1.5 mcg/kg/week plus	RCT, MC, OL Patients 18-60 years of age with hepatitis C genotype 1 who were treatment-naïve	N=595 72 weeks	Primary: Sustained virologic response (SVR) and viral breakthrough	Primary: All 4 boceprevir groups had significantly better SVR than the PR48 control group. In the 28-week treatment groups, the SVR was 56% in the PR4/PRB24 group (P=0.005 vs control) and 54% in the PRB28 group (P=0.013 vs control). In the 48-week treatment groups, the SVR was 75% in the PR4/PRB44 group (P<0.0001 vs control) compared with 67% in the PRB48 group (P<0.0001 vs control). There were significantly lower relapse rates in the 48-week treatment groups compared with PR48 control (PRB48, P=0.0079; PR4/PRB44, P=0.0002). Low-dose ribavirin was associated with a high rate of viral breakthrough (27%), and a rate of relapse (22%) similar to control (24%). The rate of breakthrough in the boceprevir lead-in groups was 4% compared with 9% in the boceprevir groups with no lead in (P=0.057). In the 28-week treatment groups, 82% of patients in the PR4/PRB24 group and 74% in the PRB28 group who had rapid virological response achieved SVR. In the 48-week treatment groups, 94% of patients assigned to PR4/PRB44 and 84% assigned to PRB48 who achieved undetectable hepatitis C virus RNA by week 4 of boceprevir achieved SVR. The most common side effects in the boceprevir group were fatigue, anemia, nausea and headache, which was similar to PR48 control. The rate of dysgeusia and anemia was higher in boceprevir groups than other groups. Treatment discontinuation was 9-19% in boceprevir studies compared to 8% in the PR48 control group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ribavirin 800-1,400 mg/day for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 44 weeks (PRB44) vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,400 mg/day plus boceprevir 800 mg 3 times a day for 28 weeks (PRB28) vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 800-1,400 mg/day plus boceprevir 800 mg 3 times a day for 48 weeks (PRB48) vs peginterferon alfa-2b 1.5 mcg/kg/week plus				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ribavirin 400-1,000 mg/day for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 48 weeks (PRB48)				
Poordad et al.[13] (2011) SPRINT-2 Peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 600-1,400 mg/day for 48 weeks (standard of care) vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 600-1,400 mg/day for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 24 weeks. If HCV RNA levels were detectable	RCT, PC, MC Patients >18 years of age with chronic infection with HCV genotype 1, and plasma HCV RNA level >of 10,000 IU/ml who were treatment-naïve	N=1,097 72 weeks	Primary: Sustained virologic response (SVR) and safety	Primary: Among non-blacks, the rate of a sustained virologic response was 40% with the standard of care and was significantly higher (P<0.001) in both boceprevir groups (67% in group 2 and 68% in group 3). Among blacks, the rate of a sustained virologic response was 23% in group 1, 42% in group 2 (P=0.04 vs group 1) and 53% in group 3 (P=0.004 vs group 1). At 4 weeks, 23% of non-blacks and 38% of blacks had a decrease of <1 $\log_{10}$, which was associated with lower rates of SVR. In group 2, 22% of patients had detectable HCV RNA levels between 8-24 weeks and received therapy for >28weeks. Of patients with detectable HCV RNA at 8 weeks 74% in group 2 and 74% in group 3 had SVR (24 weeks vs 44 weeks boceprevir therapy). Fatigue, headache and nausea were the most common adverse events and dysgeusia occurred twice as often in the boceprevir groups. Anemia was reported in 29% of controls and 49% of boceprevir groups. Grades 1, 2, 3, and 4 anemias in control groups were 36%, 17%, 2% and 0%, respectively compared to 43%, 31%, 3% and 1%, respectively in boceprevir groups. A total of 13% of controls and 21% of boceprevir patients required dose reduction due to anemia. Erythropoietin was administered in 24% of controls and 43% of boceprevir patients. Significantly more patients in the boceprevir groups 24% (group 2) and 25% (group 3) had grade 3 neutropenia (ANC 500-750) vs control 14% (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
at any visit from week 8 to week 24, peginterferon-ribavirin was continued from week 28 through week 48 (group 2) vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 600-1,400 mg/day for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 44 weeks (group 3)				
Bacon et al.[14] (2011) RESPOND-2 Peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 600-1,400 mg/day for 48 weeks (group 1) vs peginterferon	RCT, DB, PC, MC Previously treated adults with HCV genotype 1 infection with responsiveness to interferon therapy for a minimum of 12weeks	N=403 72 weeks	Primary: Sustained virologic response (SVR) Secondary: Early response and relapse rate	Primary: Overall SVR rates were 21%, compared to 59% and 66% in groups 1, 2, and 3, respectively (P<0.001). Secondary: Response rates at the end of treatment were 70% and 77% in group 2 and group 3, respectively compared to 31% in group 1. Relapse rates were significantly lower in group 2 (15%) and group 3 (12%) compared to group 1 (32%). Viral breakthrough occurred in 1% of patients in group 1, 6% of patients in group 2 and 4% of patients in group 3. In prior relapse patients, SVR rates were 29%, 69% and 75% in groups 1,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
alfa-2b 1.5 mcg/kg/week plus ribavirin 600-1,400 mg/day for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 32 weeks. Patients with an undetectable HCV RNA level at weeks 8 and 12 completed therapy at week 36, whereas those with a detectable HCV DNA level at week 8 (but an undetectable level at week 12) received peginterferon-ribavirin for an additional 12 weeks (group 2) vs peginterferon alfa-2b 1.5 mcg/kg/week plus ribavirin 600-1,400 mg/day for 4 weeks, followed by peginterferon				2 and 3, respectively. In prior non-response patients, SVR rates were 7%, 40% and 50% in groups 1, 2 and 3, respectively. A total of 15%, 28% and 27% of patients in groups 1, 2 and 3, respectively had a poor response to peginterferon. Of these patients, SVR was achieved in 0%, 33% and 34% of patients in groups 1, 2 and 3, respectively. Patients with a good response to peginterferon achieved SVR rates of 25%, 73% and 79% in groups 1, 2 and 3 respectively. At week 8, the number of patients with undetectable HCV RNA levels was 9%, 46% and 52% in groups 1, 2 and 3, respectively. There was no difference in SVR rates between groups 2 and 3 (OR 1.4, 95% CI, 0.9-2.2). Factors significantly associated with achieving SVR: randomization to boceprevir group 2 or 3(P<0.001), previous relapse (P<0.001), low viral load at baseline (P=0.02), absence of cirrhosis (P=0.04). A total of 61% of patients discontinued therapy at week 12 due to no response in group 1 compared to 22% and 18% in group 2 and 3, respectively. Anemia occurred in 43-46% of boceprevir groups compared to 20% in the control group (P<0.001). More patients discontinued therapy due to adverse events in the boceprevir-treated groups (8% to 12%) than in the control group (2%; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 44 weeks (group 3)				
McHutchison et al.[21] (2009) PROVE1 Peginterferon alfa-2a 180 mcg/week, ribavirin 1,000-1,200 mg/day and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 12 weeks (T12PR24) vs peginterferon alfa-2a 180 mcg/week, ribavirin 1,000-1,200 mg/day and telaprevir 1,250 mg as a single dose, then 750 mg	RCT, MC, DB, PC Patients 18 to 65 years of age with chronic genotype 1 HCV infection who were treatment-naïve	N=263 72 weeks	Primary: Sustained virologic response (SVR), rapid virologic response rates, relapse rates, viral breakthrough, safety	Primary: The SVR rate was 61% in the T12PR24 group compared to 41% in the PR48 group (P=0.02).The SVR rates were 67% in the T12PR48 group (P=0.002 and P=0.51 for the comparison with the PR48 group and the T12PR24 group, respectively) and 35% in the T12PR12 group. In a subgroup of black patients, rates of SVR were 11% in the PR48 group and 44% in the telaprevir-based groups. Rates of rapid virologic response were higher with telaprevir- based therapy than without it (P<0.001 for each comparison). At the end of treatment, 75% of patients in the PR48 group and 76% of those in the telaprevir-based groups had normal ALT values. Only 2% of patients in the T12PR24 group had a relapse compared to 6% of patients in the T12PR48 group and 33% of patients in the T12PR12 group. In the PR48 group, 23% of patients had a relapse. Among the telaprevir-treated patients, 7% of patients had viral breakthrough. The most common adverse events were rash, pruritus, nausea, and diarrhea with telaprevir. The proportion of patients who discontinued treatment because of an adverse event was higher in the three telaprevir-based treatment groups (21%) than in the PR48 group (11%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 36 weeks (T12PR48) vs peginterferon alfa-2a 180 mcg/week, ribavirin 1,000-1,200 mg/day and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for 12 weeks (T12PR12) vs peginterferon alfa-2a 180 mcg/week and ribavirin 1,000-1,200 mg/day for 48 weeks (PR48)				
Hézode et al.[22] (2009) PROVE2 Peginterferon alfa-2a 180	RCT, MC, DB, PC Patients 18 to 65 years of age with chronic genotype 1 HCV infection who were treatment-	N=388 72 weeks	Primary: Median time to undetectable HCV RNA level, sustained virologic response (SVR), rapid virologic	Primary: The median time to an undetectable HCV RNA level was 113 days in the PR48 group, 28 days in the T12PR24 group, 22 days in the T12PR12 group, and 29 days in the T12P12 group. At week 4, HCV RNA levels were undetectable in 69% of patients in the T12PR24 group, 80% in the T12PR12 group, and 50% in the T12P12

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg/week, ribavirin 1,000-1,200 mg/day and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 12 weeks (T12PR24) vs peginterferon alfa-2a 180 mcg/week, ribavirin 1,000-1,200 mg/day and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for 12 weeks (T12PR12) vs peginterferon alfa-2a 180 mcg/week and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for	naïve		response rates, relapse rates, viral breakthrough, safety	group (vs 13% in the PR48 group, P<0.001 for each comparison). At week 12, HCV RNA levels were undetectable in 73% of patients in the T12PR24 group (vs 43% in the PR48 group, P<0.001), 80% in the T12PR12 group (P<0.001), and 62% in the T12P12 group (P=0.02). At the end of treatment, HCV RNA levels were higher in both groups receiving all three study drugs (70% in the T12PR24 group and 80% in the T12PR12 group) and in the T12P12 group (62%) than in the PR48 group (55%). The rate of SVR for the PR48 group was 46%. The rate of SVR for the combined T12P12 and T12PR12 groups was 48% (P=0.89 for the comparison with the PR48 group). In the T12PR24 group, SVR was achieved in 69% of patients (P=0.004 vs PR48). The rate of SVR was not significantly higher in the T12PR12 group or the T12P12 group than in the PR48 group. In the T12PR12 group, there was a SVR in 60% of patients (P=0.12 vs PR48). In the T12P12 group, a SVR was achieved in 36% of patients (P=0.20 vs PR48). The difference between the rates in the T12PR12 group and the T12P12 group was significant (P=0.003). By week 12, viral breakthrough occurred in 1% of patients in the PR48 group, 24% of patients in the T12P12 group, 1% of patients in the T12PR12 group, and 5% of patients in the T12PR24 group. Relapse occurred in 14% of patients in the T12PR24 group, 30% of patients in the T12PR12 group, 48% of patients in the T12P12 group, and 22% of patients in the PR48 group. In the T12PR24 group, the relapse rate among those who had undetectable HCV RNA at weeks 4 and 12 was 7%. Pruritus and rash were more frequent in the telaprevir groups than in the control group. Telaprevir administration also affected hemoglobin levels during the treatment period. Twenty-eight patients (12%) in the telaprevir-based groups discontinued the study treatment because of adverse events compared with 7% in the control group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12 weeks (T12P12) vs peginterferon alfa-2a 180 mcg/week and ribavirin 1,000-1,200 mg/day for 48 weeks (PR48)				
Jacobson et al.[16] (2011) ADVANCE Peginterferon alfa-2a 180 mcg/week, ribavirin 1,000-1,200 mg/day and telaprevir 750 mg 3 times daily for 12 weeks (T12PR) vs peginterferon alfa-2a 180 mcg/week, ribavirin 1,000-1,200 mg/day and telaprevir 750 mg 3 times daily for 8 weeks, followed by peginterferon alfa-2a and	RCT, DB, PC, MC Patients 18 to 70 years of age with hepatitis C virus genotype 1 infection with evidence of chronic hepatitis who were treatment-naïve	N=1,088 72 weeks	Primary: Sustained virologic response (SVR), relapse rate Secondary: Proportion of patients with undetectable HCV RNA at week 72; at week 4, week 12, or both weeks 4 and 12; at the end of treatment; and 12 weeks after the last planned dose of treatment, relapse, rate of virologic failure, adverse events	Primary: The proportion of patients achieving SVR was significantly higher in the telaprevir groups (75%, T12PR and 69%, T8PR) compared to 44% in the PR group (P<0.001 for both telaprevir groups vs PR). Secondary: Undetectable HCV RNA levels at 72 weeks were present in 73% and 67% of T12PR and T8PR groups, respectively compared to 44% in the PR group (P<0.001 for both comparisons). Undetectable HCV RNA levels at 4 weeks were present in 68%, 55% and 9% of the 3 groups, respectively. Undetectable HCV RNA levels at 4 and 12 weeks were present in 58%, 57% and 8% of the 3 groups, respectively. Of the extended rapid virologic response, patients assigned to 24 weeks of therapy, 89% and 83% in the T12PR and T8PR groups met criteria for SVR. A total of 62% and 58% of black patients in the T12PR and T8PR groups, respectively had SVR compared to 25% in the PR group. Relapse occurred in 9% of the T12PR and T8PR groups compared to 28% in the PR group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ribavirin for 4 weeks (T8PR) vs peginterferon alfa-2a 180 mcg/week and ribavirin 1,000-1,200 mg/day for 48 weeks (PR) Patients in the T12PR/T8PR groups who had a rapid virologic response received 12 additional weeks of peginterferon-ribavirin. Patients in the T12PR/T8PR groups who had detectable HCV RNA at week 4 or 12 received 36 additional weeks of peginterferon-ribavirin.				Rates of virologic failure were lower in the telaprevir groups (8%-13%) compared to the PR group (32%). Nausea, diarrhea, pruritus, rash and anemia were at least 10% greater in telaprevir treated patients than in the PR group. A total of 10% of telaprevir patients discontinued the study due to adverse events compared to 7% in the PR group. Anemia and rash were the 2 most common adverse events leading to discontinuation in the telaprevir groups.
Marcellin et al.[18] (2011) Peginterferon alfa-2a 180 mcg/week, ribavirin 1,000-	RCT, OL, MC Patients 18 to 65 years of age with chronic HCV genotype 1 infection who were	N=161 72 weeks	Primary: Sustained virologic response (SVR), viral breakthrough, relapse	Primary: Rapid virologic response (RVR) was 80.0%, 69.0%, 82.5%, and 66.7% in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively. RVR in the pooled q8h group was similar to that in the pooled q12h group (74.4% vs 74.7%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1,200 mg/day and telaprevir 750 mg 3 times daily (q8h alfa-2a) vs peginterferon alfa-2b 1.5 mcg/kg/week, ribavirin 800-1,200 mg/day and telaprevir 750 mg 3 times daily (q8h alfa-2b) vs peginterferon alfa-2a 180 mcg/week, ribavirin 1,000-1,200 mg/day and telaprevir 1,125 mg every 12 hours (q12h alfa-2a) vs peginterferon alfa-2b 1.5 mcg/kg/week, ribavirin 800-1,200 mg/day and telaprevir 1,125 mg every 12 hours (q12h	treatment-naïve			RVR rate in the pooled peginterferon alfa-2a group was higher than in the pooled peginterferon alfa-2b group (81.3% vs 67.9%). At week 12, the percentage of patients with undetectable HCV RNA increased to 92.5%, 92.9%, 82.5%, and 84.6%, in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively. SVR was similar in all 4 treatment groups: 85.0%, 81.0%, 82.5%, and 82.1% in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively. SVR rate was 82.9% in the pooled telaprevir q8h group and 82.3% in the pooled telaprevir q12h group. SVR rate was 83.8% in the pooled peginterferon alfa-2a group and 81.5% in the pooled peginterferon alfa-2b group. Relapse was observed in 9 patients: 3, 2, 3, and 1 in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively. A total of 8.7% of viral breakthroughs were observed in 1, 6, 3, and 4 patients in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively. There were no significant adverse events or deaths during the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
alfa-2b) Patients received 12 weeks of treatment with telaprevir and peginterferon alfa/ribavirin, followed by peginterferon alfa/ribavirin alone for 12 or 36 weeks, based on on-treatment virologic response criteria. Patients with undetectable plasma HCV RNA at week 4 through week 20 were scheduled to receive a total of 24 weeks of therapy. Patients not meeting this criterion were assigned to receive a total of 48 weeks of treatment.				
Sherman et al.[19] (2011) ILLUMINATE Peginterferon alfa-2a 180 mcg/week,	RCT, MC, OL Patients 18 to 70 years of age with chronic HCV genotype 1 infection who were treatment-naïve	N=540 72 weeks	Primary: Sustained virologic response (SVR)	Primary: Overall, 72% of patients had a rapid virologic response (RVR) at week 4 and 65% of patients had an extended rapid virologic response. The overall rate of SVR was 72%. A total of 92% of patients in the T12PR24 group and 88% of patients in the T12PR48 group had SVR (95% CI, −2 to 11). Of those who did not have an extended rapid virologic response in the T12PR48 group, 64%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ribavirin 1,000 to 1,200 mg/day and telaprevir 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 12 weeks (T12PR24) vs peginterferon alfa-2a 180 mcg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 36 weeks (T12PR48)				had SVR. Of the remaining who prematurely discontinued treatment before week 20, 23% had SVR. A total of 99% of patients in the 24-week group completed the treatment compared to 74% in the 48-week group (P<0.001). The relapse rates were 6% with T12PR24 and 3% with T12PR48, with an overall relapse rate of 8%. The HCV RNA level was undetectable at 72 weeks after the start of treatment in 70% of patients overall (87.0% in the T12PR24 group and 87.5% in the T12PR48 group; 95% CI, −7.7 to 6.8). A total of 69% of patients with a high viral load had SVR; 63% of patients with bridging fibrosis or cirrhosis had SVR. Among patients with an extended rapid virologic response and bridging fibrosis or cirrhosis, rates of sustained virologic response were 82% in the T12PR24 group and 88% in the T12PR48 group (P=NS). Overall, 74% of white patients versus 60% of black patients had SVR (P=0.02). Virologic failure during the treatment phase was uncommon (8% of the overall population, 2% of patients in the T12PR24 group, and 3% of the patients in the T12PR48 group; P=0.22). A total of 9% of patients had serious adverse events. Anemia was reported in 2% of patients. A total of 2% of patients in the T12PR24 group, as compared with 10% of the patients in the T12PR48 group who had had an extended rapid virologic response, had serious adverse events (P=0.005). Fatigue was the most common adverse event (68%), followed by pruritus (51%), nausea (47%), anemia (39%), headache (38%), rash (37%), insomnia (34%), diarrhea (30%), and influenzalike illness (26%). During the telaprevir treatment phase, 7% of all patients discontinued treatment; 1% was attributable to rash events and 1% to anemia events.
McHutchinson et al.[15]	RCT	N=465	Primary: Sustained virologic	Primary: SVR rates were significantly higher in the telaprevir-treated groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) PROVE3 Peginterferon alfa-2a 180 mcg/week, ribavirin 1,000-1,200 mg/day and telaprevir 1,125 mg as a single dose, then 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 12 weeks (T12PR24) vs peginterferon alfa-2a 180 mcg/week, ribavirin 1,000-1,200 mg/day and telaprevir 1,125 mg as a single dose, then 750 mg 3 times daily for 24 weeks, followed by peginterferon alfa-2a and ribavirin for 24 weeks (T24PR48)	Patients 18 to 70 years of age with chronic hepatitis C virus infection genotype 1 who had previously been treated for HCV infection with peginterferon alfa and ribavirin but did not have a sustained virologic response	72 weeks	response (SVR), early response, virologic breakthrough, relapse rate	(T12PR24, 51%; T24PR48, 53%; and T24P24, 24%) compared to the PR48 group (14%; P<0.001, P<0.001, P=0.02, respectively). The response rates at the end of treatment period, at week 4 and at week 12 were all higher in the telaprevir groups compared to the control group. Relapse rates were 30%, 13% and 53% in the T12PR24, T24PR48 and T24P24 groups, respectively compared to 53% in the PR48 group. Virologic breakthrough at week 24 was 13%, 12% and 32% in the T12PR24, T24PR48 and T24P24 groups, respectively compared to 3% in the PR48 group. In the telaprevir groups, those with breakthrough were mostly non-responders. In patients with a previous nonresponse, SVR rates were 39%, 38% and 11% in the T12PR24, T24PR48, and T24P24 groups, respectively compared to 9% in the PR48 group. In patients with a previous relapse, SVR rates were 69%, 76% and 42% in the T12PR24, T24PR48 and T24P24 groups, respectively compared to 20% in the PR48 group. SVR was significantly associated with T12PR24 and T24PR48 groups, an undetectable HCV RNA level during previous PR therapy, and low baseline viral load (<800,000 IU/ml). Rash and pruritus were more common in the telaprevir groups than PR48 group. The incidence was 50% in T12PR24 and 60% in T24PR48 groups compared to 20% in PR48. Severe grade 3 rash occurred in 5% of T12PR24, 4% of T245PR48 and 3% of T24P24 compared to 0% in PR48.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs peginterferon alfa-2a 180 mcg/week and telaprevir 1,125 mg as a single dose, then 750 mg 3 times daily for 24 weeks (T24P24) vs peginterferon alfa-2a 180 mcg/week and ribavirin 1,000-1,200 mg/day for 48 weeks (PR48)				
Zeuzem et al.[17] (2011) REALIZE Peginterferon alfa-2a 180 mcg/week, ribavirin 1,000-1,200 mg/day and telaprevir 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for	RCT, MC Patients 18 to 70 years of age with chronic HCV genotype 1 infection who did not have a sustained virologic response to one previous course of peginterferon plus ribavirin	N=663 72 weeks	Primary: Proportion of patients with a previous relapse or a lack of previous response who had a sustained virologic response (SVR)	Primary: Overall SVR rates were 64% in T12PR48, 66% in lead-in T12PR48 and 17% in PR48 (P<0.001 for both telaprevir groups vs control). In patients with a previous relapse, the SVR was 83% 88%, and 24% in T12PR48, lead-in T1248 and PR48, respectively (P<0.001). Virologic failure was 1% with telaprevir vs 26% in the control group. In patients with no previous virologic response or partial response, the SVR was 41%, 41% and 9% in the T12PR48, lead-in T12PR48 and PR48, respectively (P<0.001). In patients with a previous partial response, the SVR was 59%, 54% and 15% in the T12PR48, lead-in T12PR48 and PR48, respectively (P<0.001). Virologic failure was 18%, 19% and 70%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
36 weeks (T12PR48) vs peginterferon alfa-2a 180 mcg/week and ribavirin 1,000-1,200 mg/day for 4 weeks, then peginterferon alfa-2a, ribavirin and telaprevir 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 32 weeks (lead-in T12PR48) vs peginterferon alfa-2a 180 mcg/week and ribavirin 1,000-1,200 mg/day for 48 weeks (PR48)				In patients with a previous non-response, the SVR was 29%, 33% and 5% in the T12PR48, lead-in T12PR48 and PR48, respectively (P<0.001). Virologic failure was 57%, 47% and 84%, respectively. In a pooled subgroup analysis of patients with previous relapse or partial response, those treated with telaprevir had a higher SVR (78%) vs control (21%; P<0.001). Adverse events occurring in >25% of telaprevir groups included fatigue, pruritus, rash, nausea, influenza like illness, anemia and diarrhea. Grade 3 adverse events occurred in 37% of telaprevir treated patients vs 22% of controls. The rate of grade 3 rash was 3% and pruritus was 1% with telaprevir vs 0% with control. A total of 4% of telaprevir-treated patients discontinued therapy due to rash vs 0% in control.
Muir et al.[20] (2011) Peginterferon alfa-2a 180 mcg/week, ribavirin 1,000 to	OL, MC Patients with chronic genotype 1 HCV infection with a prior response to peginterferon alpha-	N=117 96 weeks	Primary: Sustained virologic response (SVR)	Primary: The overall rate of SVR was 59%. The SVR rate was highest among patients who previously relapsed (97%), prior viral breakthrough patients (75%), and prior partial response patients (55%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1,200 mg/day and telaprevir 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 12 or 36 weeks If patients achieved extended rapid virologic response (eRVR) with triple therapy, they would complete a 24-week course with 12 more weeks of peginterferon alpha-2a and ribavirin alone. If patients did not achieve eRVR with triple therapy, they would complete a 48-week course with 36 more weeks of peginterferon alpha-2a and ribavirin.	2a and ribavirin			Among prior null responders, the overall SVR rate was 37% with 56% of patients in the 48-week treatment group and 17% of patients in the 24-week treatment group. The overall relapse rate was 16%. Discontinuations due to the week 4 stopping rule were more frequent in patients assigned to the 24- week regimen (10%) than in those assigned to the 48-week regimen (3%). Eleven cases of viral breakthrough occurred in patients with previous null response, and seven of the 15 occurred during the first 12 weeks of retreatment that included telaprevir. Rash occurred in 27% of patients during the first 12 weeks of treatment. Pruritus occurred in 35% of patients during the telaprevir treatment phase. Decreases in hemoglobin levels, increases in uric acid levels, and increases in total bilirubin levels were more common during the telaprevir treatment phase. Adverse events led to discontinuation of all study drugs in 9% of patients and 7% of patients during the telaprevir treatment phase.

Study abbreviations: CI=confidence interval, DB=double-blind, MC=multicenter, PC=placebo-controlled, RCT=randomized controlled trial, RR=relative risk
Other abbreviations: ALT=alanine aminotransferase, HIV=human immunodeficiency virus, SVR=sustained virologic response

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 9. Relative Cost of the HCV Protease Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Boceprevir	capsule	Victrelis®	$$$$$	N/A
Telaprevir	tablet	Incivek®	$$$$$	N/A

N/A=Not available

X. Conclusions

The HCV protease inhibitors are approved for use in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C virus (HCV) genotype 1 infection.[1-5] This is a new AHFS class, which has not been reviewed previously. There are no generic products available.

According to the 2011 AASLD guidelines, the optimal treatment for chronic HCV genotype 1 infection is boceprevir or telaprevir in combination with peginterferon alfa and ribavirin.[8] They do not give preference to one HCV protease inhibitor over another. Refer to Table 2 and Table 7 for specific recommendations on dosage, duration of treatment, and criteria for discontinuation of therapy in treatment-naïve patients. Retreatment with boceprevir or telaprevir is recommended for patients who had virological relapse or were partial responders after prior treatment with interferon alfa or peginterferon alfa and/or ribavirin.[8] Retreatment with telaprevir may be considered for prior null responders to interferon alfa or peginterferon alfa and/or ribavirin. Response-guided therapy with boceprevir or telaprevir can be considered for relapsers, may be considered for partial responders, but is not recommended for null responders. Patients who fail to have a virological response, experience

virological breakthrough, or relapse with one HCV protease inhibitor should not be retreated with the other HCV protease inhibitor.

In clinical trials, boceprevir and telaprevir improved SVR rates by ≥10% when added to peginterferon alfa and ribavirin therapy.[12-22] The improved responses were maintained in difficult-to-treat groups, including patients who failed previous therapy, genotype 1 patients, and African-American patients. The HCV protease inhibitors may also offer a method to reduce the overall length of therapy in early virologic responders. Whether one agent has clinical advantages over the other still remains to be determined.

The most frequently reported adverse events with boceprevir in clinical trials were fatigue, anemia, nausea, headache and dysgeusia. In telaprevir trials, the most frequently reported adverse events were rash, anemia, fatigue, pruritus, nausea and vomiting. The addition of boceprevir or telaprevir to peginterferon alfa and ribavirin therapy also increased the risk of anemia.

There is insufficient evidence to support that one brand HCV protease inhibitor is safer or more efficacious than another. The optimal treatment for chronic HCV genotype 1 infection is boceprevir or telaprevir in combination with peginterferon alfa and ribavirin. The HCV protease inhibitors must not be used as monotherapy due to the development of resistance. Since there are very specific criteria that must be met when initiating therapy, these agents should be managed through the medical justification portion of the prior authorization process.

Therefore, boceprevir (Victrelis®) and telaprevir (Incivek®) offer significant clinical advantages in general use over the other brands, generics and OTC products in the same class (if applicable), but are comparable to each other.

XI. Recommendations

No brand HCV protease inhibitor 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antivirals, Miscellaneous
AHFS Class 081892
May 9, 2012

I. Overview

Foscarnet is approved for the treatment of cytomegalovirus (CMV) retinitis in patients with the acquired immunodeficiency syndrome (AIDS).[1-3] It is also approved for the treatment of acyclovir-resistant mucocutaneous herpes simplex virus infections in immunocompromised patients.

Foscarnet exerts its antiviral activity by a selective inhibition at the pyrophosphate binding site on virus-specific DNA polymerases, which halts DNA chain elongation.[1-3] It is virostatic and is not structurally related to any other antiviral agent currently on the market. Foscarnet has poor oral bioavailability and must be administered intravenously. Following administration, serum levels can vary considerably.[1-4] Patients receiving foscarnet need to be carefully monitored since adverse events occur frequently and may be potentially serious.[4] Major toxicities associated with foscarnet include renal impairment, electrolyte disturbances and seizures.

The miscellaneous antivirals that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Foscarnet is available in a generic formulation. This class was last reviewed in November 2009.

Table 1. Antivirals, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Foscarnet	injection	N/A	foscarnet

PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous antivirals are summarized in Table 2.

Table 2. Treatment Guidelines Using the Antivirals, Miscellaneous

Clinical Guideline	Recommendation(s)
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[6] (2008)**	Treatment of CMV Retinitis • Oral valganciclovir, IV ganciclovir, IV ganciclovir followed by oral valganciclovir, IV foscarnet, IV cidofovir, and the ganciclovir intraocular implant coupled with valganciclovir are all effective treatments for CMV retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, IV, and local options. • The choice of initial therapy for CMV retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in terms of protecting vision, and thus clinical judgment must be used when choosing a regimen. Management of CMV Retinitis Treatment Failures • When patients relapse while receiving maintenance therapy, induction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of

Clinical Guideline	Recommendation(s)
	time, and the majority of specialists recommend this approach for initial treatment of relapsed disease. • Changing to an alternative drug at the time of first relapse typically does not result in better control of the retinitis but should be considered if drug resistance is suspected or if side effects or toxicities interfere with optimal courses of the initial agent. • The combination of ganciclovir and foscarnet is generally more effective than systemic therapy with either agent alone for patients with relapsed retinitis but is accompanied by greater toxicity; this approach might be considered for patients who are not candidates for other alternatives. <u>Preventing Recurrence of CMV</u> • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) is recommended for life, unless immune reconstitution occurs as a result of ART. • Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir or valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, parenteral cidofovir, and (for retinitis only) ganciclovir administration through intraocular implant. <u>Treatment of HSV Disease</u> • Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for 5–10 days. Severe mucocutaneous HSV lesions are best treated initially with IV acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed. • Genital HSV infection should be treated with oral valacyclovir, famciclovir, or acyclovir for 5–14 days. Short-course therapy (1, 2, or 3 days) should not be used in patients with HIV infection. • Most recurrences of genital herpes can be prevented by use of daily anti-HSV therapy, and this is recommended for persons who have frequent or severe recurrences. The option for suppressive therapy should be discussed with every HSV-2-infected patient. Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in HIV-infected persons or twice-daily regimens with acyclovir or famciclovir should be used. <u>Management of HSV Treatment Failure</u> • The treatment of choice for acyclovir-resistant HSV is IV foscarnet. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21–28 days or longer might be required.
Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines[7] (2010)**	<u>Genital Herpes</u> • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized trials have indicated that three antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir. • Topical therapy with antiviral drugs offers minimal clinical benefit, and its use is discouraged. • Foscarnet is frequently effective for treatment of acyclovir-resistant genital herpes in immunocompromised individuals.

Clinical Guideline	Recommendation(s)
British Association for Sexual Health and HIV (BASHH): **National Guideline for the Management of Genital Herpes[5] (2007)**	Genital Herpes • Oral antiviral drugs are indicated within 5 days of the start of the episode and while new lesions are still forming. • Antiviral therapy does not alter the natural history of the disease. • Topical agents are less effective than oral agents. • Combined oral and topical treatment is of no benefit. • Intravenous therapy is indicated only when the patient cannot swallow or tolerate oral medication because of vomiting. Genital Herpes with HIV Infection • Standard systemic antiviral drugs, as used to treat genital herpes in HIV-uninfected patients, have been shown to successfully treat genital herpes in patients with HIV. • Resistance to antiherpes drugs is more common in those with HIV co-infection and is associated with treatment failure of genital herpes. • Oral acyclovir, valacyclovir, and famciclovir are recommended for initial and suppressive treatment of genital herpes. • In severe cases, initiating therapy with acyclovir 5–10 mg/kg body weight IV every 8 hours may necessary. • Systemic therapy with either foscarnet or cidofovir is generally preferred to treat drug resistant herpes in those with HIV.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antivirals are noted in Table 3. 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 3. FDA-Approved Indications for the Antivirals, Miscellaneous[1-3]

Indication	Foscarnet
Treatment of acyclovir-resistant mucocutaneous herpes simplex virus infections in immunocompromised patients	✔
Treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antivirals are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Antivirals, Miscellaneous[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (Hours)
Foscarnet	N/A	14-17	Not reported	Renal (73-94)	3-6

V. Drug Interactions

No significant drug interactions with the miscellaneous antivirals have been reported.[1] Since foscarnet decreases serum concentrations of ionized calcium, concurrent treatment with other drugs known to influence serum calcium concentrations should be used with caution.[1-3] Fatalities have been reported in post-marketing surveillance during concomitant therapy with foscarnet and pentamidine. Because of the tendency of foscarnet to cause renal impairment, the use of foscarnet in combination with potentially nephrotoxic drugs (e.g., aminoglycosides, amphotericin B and intravenous pentamidine) should be avoided unless the potential benefits outweigh the risks to the patient.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antivirals are listed in Table 5. The boxed warning for foscarnet is listed in Table 6.

Table 5. Adverse Drug Events (%) Reported with the Antivirals, Miscellaneous[1-5]

Adverse Events	Foscarnet
Cardiovascular	
Cardiac arrest	<1
Chest pain	1-5
Edema	1-5
Electrocardiogram (ECG) abnormalities	<5
Flushing	1-5
Hypertension	1-5
Hypotension	1-5
Palpitation	1-5
QT_c prolongation	<1
Ventricular arrhythmia	<1
Central Nervous System	
Aggressiveness	1-5
Agitation	1-5
Amnesia	1-5
Anxiety	≥5
Aphasia	1-5
Ataxia	1-5
Coma	<1
Confusion	≥5
Coordination abnormal	1-5
Dementia	1-5
Depression	≥5
Dizziness	≥5
EEG abnormal	1-5
Fatigue	≥5
Fever	65
Hallucinations	1-5
Headache	26
Hypoesthesia	≥5
Insomnia	1-5
Malaise	≥5
Meningitis	1-5
Nervousness	1-5
Paresthesia	≥5
Peripheral neuropathy	≥5
Seizure	8

Adverse Events	Foscarnet
Somnolence	1-5
Stupor	1-5
Tremor	1-5
Dermatological	
Erythema multiforme	<1
Erythematous rash	1-5
Maculopapular rash	1-5
Pruritus	1-5
Seborrhea	1-5
Skin discoloration	1-5
Skin ulceration	1-5
Stevens-Johnson syndrome	<1
Rash	≥5
Toxic epidermal necrolysis	<1
Vesiculobullous eruptions	<1
Gastrointestinal	
Abdominal pain	≥5
Anorexia	≥5
Constipation	1-5
Diarrhea	30
Dyspepsia	1-5
Dysphasia	1-5
Flatulence	1-5
Melena	1-5
Nausea	47
Pancreatitis	1-5
Rectal hemorrhage	1-5
Taste perversion	1-5
Ulcerative stomatitis	1-5
Vomiting	26
Weight loss	1-5
Xerostomia	1-5
Genitourinary	
Acute renal failure	1-5
Albuminuria	1-5
Dysuria	1-5
Hematuria	<1
Nocturia	1-5
Polyuria	1-5
Renal calculus	<1
Urinary retention	1-5
Urinary tract infection	1-5
Hematologic	
Anemia	33
Granulocytopenia	17
Leukopenia	≥5
Lymphadenopathy	1-5
Neutropenia	<1
Pancytopenia	<1
Thrombocytopenia	1-5
Thrombosis	1-5
Laboratory Test Abnormalities	
Abnormal hepatic function	1-5
Acidosis	1-5

Adverse Events	Foscarnet
Alkaline phosphatase increased	1-5
ALT increased	1-5
Amylase increased	<1
AST increased	1-5
BUN increased	1-5
Creatine phosphokinase increased	<1
GGT increased	<1
Hypocalcemia	15-30
Hypokalemia	16-48
Hypomagnesemia	15-30
Hyponatremia	1-5
Hypophosphatemia	8-26
Hypoproteinemia	<1
LDH increased	1-5
Musculoskeletal	
Arthralgia	1-5
Back pain	1-5
Involuntary muscle contractions	≥5
Leg cramps	1-5
Myalgia	1-5
Myopathy	<1
Myositis	<1
Rhabdomyolysis	<1
Rigors	≥5
Weakness	≥5
Respiratory	
Bronchospasm	1-5
Cough	≥5
Dyspnea	≥5
Hemoptysis	1-5
Pharyngitis	1-5
Pneumonia	1-5
Pneumothorax	1-5
Rhinitis	1-5
Sinusitis	1-5
Stridor	1-5
Other	
Conjunctivitis	1-5
Dehydration	<1
Diabetes insipidus	<1
Diaphoresis	≥5
Eye pain	1-5
Flu-like syndrome	1-5
Hepatic function abnormal	1-5
Infection	≥5
Injection site pain	1-5
Malignancies	1-5
Pain	≥5
Sepsis	≥5
SIADH	<1
Thirst	1-5
Vision abnormalities	≥5

Table 6. Boxed Warning for Foscarnet[1]

WARNING
Renal impairment is the major toxicity of foscarnet. Frequent monitoring of serum creatinine, with dose adjustment for changes in renal function, and adequate hydration with administration of foscarnet, is imperative. Seizures, related to alterations in plasma minerals and electrolytes, have been associated with foscarnet treatment. Therefore, patients must be carefully monitored for such changes and their potential sequelae. Mineral and electrolyte supplementation may be required. Foscarnet is indicated for use only in immunocompromised patients with CMV retinitis and mucocutaneous acyclovir-resistant HSV infections.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antivirals are listed in Table 7.

Table 7. Usual Dosing Regimens for the Antivirals, Miscellaneous[1]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Foscarnet	Acyclovir-Resistant HSV Infections: 40 mg/kg every 8 to 12 hours for 2 to 3 weeks or until healed CMV Retinitis: Induction: 90 mg/kg every 12 hours or 60 mg/kg every 8 hours for 2 to 3 weeks depending on clinical response Maintenance: 90 to 120 mg/kg/day	Safety and efficacy in children have not been established.	Injection: 24 mg/ml

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antivirals are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Antivirals, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cytomegalovirus Retinitis				
AIDS Clinical Trials Group[9] (1996) Foscarnet 90 mg/kg IV every 12 hours for 2 weeks (induction), followed by a maintenance dose of 120 mg/kg per day vs ganciclovir 5 mg/kg IV every 12 hours for 2 weeks (induction) followed by a maintenance dose of 10 mg/kg per day vs continuation of previous maintenance therapy plus induction with the	MC, OL, RCT Patients with AIDS and active or relapsed CMV retinitis despite previous treatment with either agent alone within the past 28 days	N=279 2.5 years	Primary: Mortality, retinitis progression, visual acuity, visual field loss, and morbidity	Primary: The mortality rate was similar among the three groups. Median survival times were as follows: foscarnet group, 8.4 months; ganciclovir group, 9.0 months; and combination therapy group, 8.6 months (P=0.89). Comparison of retinitis progression revealed that combination therapy was the most effective regimen for controlling the retinitis. The median times to retinitis progression were as follows: foscarnet group, 1.3 months; ganciclovir group, 2.0 months; and combination therapy group, 4.3 months (P<0.001). The rates of visual field loss were as follows: foscarnet group, 28 degrees per month; ganciclovir group, 18 degrees per month; combination therapy group, 16 degrees per month (P=0.009). The rates of increase of retinal area involved by CMV were as follows: foscarnet group, 2.47% per month; ganciclovir group, 1.40% per month; and combination therapy group, 1.19% per month (P=0.04). Side effects were similar among the 3 treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
other drug (either ganciclovir or foscarnet) for 2 weeks followed by maintenance therapy with both drugs combined				
Palestine et al.[10] (1991) Foscarnet 60 mg/kg TID day for 3 weeks (induction) followed by a maintenance dose of 90 mg/kg once a day vs no therapy (delayed treatment, control group)	MC, RCT Patients with previously untreated AIDS and CMV at low risk for loss of visual acuity were examined weekly to evaluate progression of retinal disease.	N=24 Variable duration	Primary: Progression of retinitis border by 750 microns or development of a new retinal lesion due to CMV Secondary: Changes in visual acuity, CMV shedding in the blood and urine, serum levels of (HIV-1) p24 antigen, and total CD4 T lymphocyte counts	Primary The mean time to progression of retinitis was 3.2 weeks in the control group vs 13.3 weeks in the treatment group (P<0.001). Secondary: Nine patients in the treatment group had positive blood cultures for CMV at entry and had clear cultures by the end of the induction period vs one in the control group (P=0.004). No reductions were seen in p24 levels in the control patients, vs a reduction of more than 50% in p24 levels for all 4 treated patients for whom follow-up levels were available. Main adverse effects of foscarnet treatment were seizures (2 patients), hypomagnesemia (9), hypocalcemia (11), and elevations in serum creatinine above 2.0 mg/dL (3). The control patients received an average of 0.2 units of blood per week compared with an average of 0.6 units of blood per week for the patients on foscarnet treatment.
AIDS Clinical Trials Group[11] (1992) Foscarnet 60 mg/kg TID for 2 weeks (induction) then 90 mg/kg QD for maintenance	MC, OL, RCT Patients with AIDS and previously untreated CMV retinitis	N=234 19 months	Primary: Progression of retinitis, visual loss, and death	Primary: Excess mortality in the ganciclovir group vs foscarnet group led the Policy and Data Monitoring Board to recommend suspension of the treatment protocol 19 months after the trial started. As of that time, 65 of the patients assigned to ganciclovir had died, vs 36 of those assigned to foscarnet (51 % vs 34 %, P=0.007; relative risk, 1.79; 95% CI: 1.17 to 2.73). The median survival was 8.5 months in the ganciclovir group vs 12.6

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ganciclovir 5 mg/kg BID (induction) then 5 mg/kg QD for maintenance				months in the foscarnet group. There was no difference between the two treatment groups in the rate of progression of retinitis (relative risk, 0.95; P=0.751).
AIDS Clinical Trials Group[12] (1997) Foscarnet 60 mg/kg TID for 2 weeks (induction) then 90 mg/kg QD for maintenance vs ganciclovir 5 mg/kg BID (induction), then 5 mg/kg daily for maintenance	MC, OL, RCT Blood and urine cultures for CMV culture were obtained from patients with newly diagnosed CMV retinitis	N=234 24 months	Primary: Clinical significance of (CMV) culture results and drug susceptibilities in CMV isolates	Primary: 207 patients had at least one positive blood or urine culture. Culture-positive rates at baseline were 45% and 71% for blood and urine, respectively. Rates decreased 3- to 10-fold after initiation of either treatment. No significant differences were found between the two treatment regimens (P=0.427). Mortality was related to both positive baseline blood and urine cultures; adjusted relative risks were 1.97 and 2.03, respectively. The association between positive blood culture and urine cultures in relation to mortality did not differ between the groups (P=0.177 and P=0.962, respectively).
AIDS Clinical Trials Group[13] (1995) Foscarnet 60 mg/kg TID for 2 weeks (induction) then 90 mg/kg QD for maintenance vs ganciclovir 5	MC, OL, RCT Patients with AIDS and previously untreated CMV retinitis Medical histories, laboratory tests, and drug treatment histories were analyzed for the first 6 months of	N=234 24 months	Primary: Incidence of hematologic and chemical abnormalities, reported symptoms, health status	Primary: Neutropenia was more common in patients assigned to ganciclovir vs those in the foscarnet group (34% vs 14%; P=0.001). Patients assigned to foscarnet reported more infusion-related symptoms (58% vs 24%; P<0.001) and, in male patients, more genitourinary symptoms (36% vs 16%; P>0.001); they also experienced a trend toward more nephrotoxic effects (13% vs 6%; P=0.082) and electrolyte abnormalities. The incidence of seizures was similar in both groups (foscarnet, 12%; ganciclovir, 9%; P=0.511).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg BID (induction) then 5 mg/kg QD for maintenance	therapy.			Patients assigned to foscarnet were more likely to be switched to the alternative treatment (foscarnet to ganciclovir, 46%; ganciclovir to foscarnet, 11%; P<0.001).
AIDS Clinical Trials Group[14] (1994) Foscarnet 60 mg/kg TID for 2 weeks (induction) then 90 mg/kg QD for maintenance vs ganciclovir 5 mg/kg BID (induction) then 5 mg/kg QD for maintenance	MC, OL, RCT Patients with AIDS and previously untreated CMV retinitis were followed at regular intervals for visual outcomes, including progression of the retinitis, visual acuity, and visual fields	N=234 24 months	Primary: Time to first progression of retinitis	Primary: The relative risk for progression of retinitis was 0.97 (ganciclovir vs foscarnet; P=0.833). The median time to first progression was 53 days with foscarnet vs 47 days with ganciclovir (P=0.997), as determined by a masked reading at a central fundus photograph reading center. By 120 days after randomization, progression was observed in 85% of patients in each treatment group. Visual acuity outcomes were similar for both groups; at 6 months, 88% of the foscarnet group and 93% of the ganciclovir group had a best-corrected visual acuity of 20/40 or better in the better eye; P=0.325. Visual field scores were similar in the two groups; in all eyes affected with CMV retinitis, there was a mean 29 degrees/month loss of visual field in foscarnet group vs a 31 degrees/month loss in ganciclovir group; P=0.674.
Herpes Simplex Virus				
Safrin et al.[15] (1991) Foscarnet (40 mg/kg IV every 8 hours) vs vidarabine (15 mg/kg/day) IV QD for 10-42 days	MC, RCT Patients with AIDS and mucocutaneous herpetic lesions unresponsive to IV therapy with acyclovir for a minimum of 10 days	N=14 42 days	Primary: Time to lesion resolution, time to complete healing	Primary: The lesions in all 8 patients assigned to foscarnet healed completely after 10-24 days of therapy. In contrast, vidarabine was discontinued because of treatment failure in all patients. The time to complete healing (P=0.01), time to 50% reductions in the size of the lesions (P=0.01) and the pain score (P=0.004), and time to the end of viral shedding (P=0.006) were all significantly shorter in the patients assigned to foscarnet.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Safrin et al.[8] (1990) Foscarnet 40 mg/kg IV every 8 hours for 10-43 days (mean 18.5)	MC, RCT Patients with HIV, received foscarnet for acyclovir-resistant HSV (34 mucocutaneous, 25 perirectal, 7 orofacial, 1 genital, 1 whitlow) that progressed despite therapy with IV(19) or high-dose oral (7) acyclovir, vidarabine (15) or ganciclovir (3)	N=26 43 days	Primary: Clinical response to foscarnet	Primary: Clinical response was noted in 81% of patients; complete re-epithelialization of HSV lesions occurred in 73%. Cessation of viral shedding was documented in all of the 11 patients who were recultured. Although adverse effects were frequent, only 3 patients discontinued therapy. Before foscarnet therapy, 14 patients received vidarabine for acyclovir-resistant HSV. The infection did not resolve in any of the vidarabine-treated patients, and therapy was discontinued in 4 (29%) patients due to toxicity.

Drug regimen abbreviations: BID=twice daily, IV=intravenous, QD=once daily, TID=three times daily
Study abbreviations: CI=confidence interval, MC=multicenter, OL=open-label, RCT=randomized controlled trial
Other abbreviations: AIDS=acquired immunodeficiency virus, CMV=cytomegalovirus

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 9. Relative Cost of the Antivirals, Miscellaneous

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

N/A=Not available

X. Conclusions

Foscarnet is approved for the treatment of cytomegalovirus (CMV) retinitis in patients with the acquired immunodeficiency syndrome (AIDS).[1-3] It is also approved for the treatment of acyclovir-resistant mucocutaneous herpes simplex virus infections in immunocompromised patients. Foscarnet is available in a generic formulation.

Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents recommend foscarnet as one of several treatment options for CMV retinitis.[6] No one regimen has been proven to have greater efficacy in terms of protecting vision.[6,9,11-14] The combination of ganciclovir and foscarnet is generally more effective than systemic therapy with either agent alone for patients with relapsed retinitis, but is accompanied by greater toxicity.[6,9] After induction therapy, secondary prophylaxis is recommended for life. Foscarnet is considered an effective treatment option for the chronic suppression of CMV retinitis.[6]

Guidelines recommend the use of foscarnet for the treatment of acyclovir-resistant genital herpes in immunocompromised individuals.[5-7] Foscarnet has been shown to be effective for the treatment of herpetic lesions in clinical trials.[8,15]

Therefore, all brand miscellaneous antivirals 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 antiviral 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Amebicides
AHFS Class 083004
May 9, 2012

I. Overview

Amebiasis is an important parasitic infection because of its worldwide distribution and serious gastrointestinal manifestations.[5] *Entamoeba histolytica* is the major pathogen responsible for amebiasis infections. It is transmitted from a human host via the fecal-oral route after ingesting the cyst from contaminated water or food. The incubation period may vary from weeks to years following exposure.[5-8] Once in the lumen of the small intestine, *E. histolytica* cysts may form into motile trophozoites and penetrate the gastrointestinal mucosa causing either an invasive intestinal infection or extraintestinal disease. Clinical manifestations of the intestinal infection range from mild abdominal discomfort and diarrhea to severe abdominal cramps, flatulence, fever, and bloody or mucoid diarrhea. If the infection spreads to extraintestinal sites, such as the liver, abscesses and other complications may develop. The trophozoite is the metabolically active form responsible for the symptoms; however, it is the *E. histolytica* cyst that is the infective form of the pathogen due to its ability to survive in the external environment, as well as the acidic conditions of the stomach.

Paromomycin is the only amebicide currently available and it is approved for the treatment of amebiasis. It is an aminoglycoside antibiotic which inhibits protein synthesis by binding to the 30S chromosome.[1-3] Paromomycin is only active against cysts in the intestinal lumen due to its poor absorption from the gastrointestinal tract. It is also approved for use as an adjunctive agent for the treatment of hepatic coma. The decline in neurologic function associated with impaired hepatic function is thought to be due to the accumulation of ammonia.[1-3,9] Antibiotics have been found to mediate this complication by inhibiting the bacteria associated with ammonia production.

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

Table 1. Amebicides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Paromomycin	capsule	N/A	paromomycin

PDL=Preferred Drug List
N/A=Not available

The amebicides have been shown to be active against the strains of microorganisms indicated in Table 2. This activity is represented by the Food and Drug Administration (FDA)-approved indications for the amebicides 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 anti-infective 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 Amebicides[1-3]

Organism	Paromomycin
Entamoeba histolytica	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Amebicides

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention (CDC): **Diagnosis and Management of Foodborne Illnesses: A Primer for Physicians and Other Health Care Professionals**[11] **(2004)**	General recommendations • Oral rehydration therapy is indicated for patients with mild-to-moderate dehydration. Intravenous therapy may be required for severe dehydration. • Selection of an appropriate antimicrobial regimen relies on clinical presentation, the isolation of the responsible pathogen, and susceptibility testing. • Once the etiology of diarrhea has been identified via microbiological testing, antimicrobial therapy should be directed at that pathogen. • The routine use of antidiarrheal agents in infants and young children is not recommended due to potentially serious adverse effects. *Entamoeba histolytica* • The recommended treatment includes the combination of metronidazole and a luminal agent (iodoquinol or paromomycin).
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Infectious Diarrhea**[10] **(2001)**	General Recommendations • Due to the risks of dehydration and malnutrition, guidelines recommend rehydration therapy as the initial management of patients with acute diarrheal illnesses. • Due to changing patterns of antimicrobial resistance, selection of antimicrobial regimens for empirical therapy should be based on prediction of the most likely pathogens(s) and knowledge of local susceptibility patterns. • Once the etiology of diarrhea has been identified via microbiological testing, antimicrobial therapy should be adjusted as necessary. Recommendations for Therapy Against Specific Pathogens • *Entamoeba histolytica* o Metronidazole 750 mg three times daily for 5-10 days plus either diiodohydroxyquin 650 mg three times daily for 20 days or paromomycin 500 mg three times daily for 7 days.

Sanford Guide to Antimicrobial Therapy[4] **(2011)**	Amebiasis (*Entamoeba histolytica*)
	• Asymptomatic cyst passer:
	  o Primary: paromomycin 25-35 mg/kg/day in 3 divided doses for 7 days or iodoquinol* 650 mg 3 times daily for 20 days
	  o Alternative: diloxanide furoate* 500 mg 3 times daily for 10 days
	• Patient with diarrhea/dysentery (mild or moderate disease):
	  o Primary: metronidazole 500-750 mg orally 3 times daily for 10 days or tinidazole 2 g once daily for 3 days, followed by either paromomycin or iodoquinol* as above to clear intestinal cysts
	• Severe intestinal disease, hepatic abscess or other extraintestinal disease:
	  o Metronidazole 750 mg IV to oral 3 times daily for 10 days or tinidazole 2 g once daily for 5 days, followed by paromomycin to clear intestinal cysts

American College of Gastroenterology (ACG): **Practice Guidelines: Hepatic Encephalopathy**[17] **(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. 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.

*Product is not commercially available in the United States.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the amebicides 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 Amebicides[1-3]

Indication	Paromomycin
Management of hepatic coma as adjunctive therapy	✔
Treatment of acute and chronic intestinal amebiasis	✔

IV. Pharmacokinetics

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

Table 5. Pharmacokinetic Parameters of the Amebicides[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (Hours)
Paromomycin	Minimal	Not reported	Not reported	Feces (~100)	Not reported

V. Drug Interactions

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

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

Generic Name(s)	Significance Level	Interaction	Mechanism
Paromomycin	2	Digoxin	Pharmacologic effects of digoxin may be increased or decreased by paromomycin due to altered bioavailability.
Paromomycin	2	Succinylcholine	The neuromuscular blocking effects of succinylcholine may be increased by paromomycin. 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 amebicides are listed in Table 7.

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

Adverse Events	Paromomycin
Central Nervous System	
Headache	<1
Ototoxicity	<1
Vertigo	<1
Dermatological	
Exanthema	<1
Pruritus	<1
Rash	<1
Gastrointestinal	
Abdominal cramps	1-10
Diarrhea	1-10
Heartburn	1-10
Nausea	1-10
Secondary enterocolitis	<1
Steatorrhea	<1
Vomiting	1-10
Other	
Eosinophilia	<1

VII. Dosing and Administration

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

Table 8. Usual Dosing Regimens for the Amebicides[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Paromomycin	Hepatic Coma: 4 g daily in divided doses for 5 to 6 days Intestinal Amebiasis: 25 to 35 mg/kg/day administered in three divided doses for 5 to 10 days	Intestinal Amebiasis: 25 to 35 mg/kg/day administered in three divided doses for 5 to 10 days	Capsule: 250 mg

VIII. Effectiveness

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

Table 9. Comparative Clinical Trials with the Amebicides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Intestinal Amebiasis Infections				
Blessmann et al.[12] (2002) Paromomycin 500 mg TID for 10 days vs diloxanide furoate* 500 mg TID for 10 days	RCT Adult patients with asymptomatic intestinal *Entamoeba histolytica* infections, confirmed via a (polymerase-chain-reaction) PCR assay	N=71 30 days	Primary: Cure rate (negative PCR assay 10 and 20 days after the termination of therapy)	Primary: Eradication at 20 days was observed in 85% of patients on paromomycin compared to 51% in the diloxanide furoate group (P=0.003).
Pamba et al.[13] (1990) Aminosidine (paromomycin)† 500 mg BID for adults and 15 mg/kg BID for children for 5 days vs etophamide‡ 600 mg BID for adults and 15 mg/kg BID for children for 5 days vs	RCT Patients between the ages of 6 and 80 with *E histolytica* intestinal infection, diagnosed via three microscopic stool examinations	N=417 60 days	Primary: Clinical cure (disappearance of all symptoms present at study onset), parasitological cure (disappearance of all parasitic forms, both invasive and noninvasive forms, from stools or ulcer scrapings), anatomical cure (healing of previous ulceration), tolerance	Primary: Eradication of invasive *E histolytica* forms was successful in all the treatment groups. At the end of treatment, the incidences of invasive and noninvasive amebic forms identified in stool samples were 0.7% and 7.7%, respectively, compared to baseline. The incidence of parasitological failure with monotherapy was 2%, 9.9% and 8% in patients treated with aminosidine, etophamide, and nimorazole, respectively, and 6.1% the nimorazole-etophamide arm. No cases of parasitological failure occurred in the nimorazole-aminosidine and etophamide-aminosidine combination groups. There were no recurrences of infection in the etophamide-aminosidine combination group, 3% in the nimorazole-aminosidine group, 6% in the aminosidine, 6.8% in the etophamide, 14.6% in the nimorazole, and 17.3% in the nimorazole-etophamide group. Ulcer cure was achieved in 97.8% in the nimorazole-aminosidine group, 95.5% in the nimorazole, 88.5% in the aminosidine, 87.8% in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
nimorazole§ 1 g BID for adults and 20 mg/kg BID for children for 5 days vs aminosidine 500 mg BID for adults and 15 mg/kg BID for children in addition to nimorazole 1 g BID for adults and 20 mg/kg BID for children for 5 days vs nimorazole 1 g BID for adults and 20 mg/kg BID for children in addition to etophamide 600 mg BID for adults and 15 mg/kg BID for children for 5 days vs etophamide 600 mg BID for adults and 15 mg/kg BID for children in				the nimorazole-etophamide, 87.5% in the etophamide, and 77% in the etophamide-aminosidine group. Clinical cure was achieved in 98%-100% of patients in all the 6 treatment groups. All the regimens were well tolerated except the etophamide-aminosidine combination, which was associated with a high incidence of severe diarrhea (76.5%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
addition to aminosidine 500 mg BID for adults and 15 mg/kg BID for children for 5 days				
Sullam et al.[14] (1986) Paromomycin 25-35 mg/kg per day divided into TID doses for 7 days	OL Homosexual men, mean age 30 years, with *E histolytica* cysts or trophozoites in stool specimens	N=114 6 weeks	Primary: Improvement or resolution of symptoms, bacteriologic cure rate, adverse effects	Primary: One week posttherapy, 70% of patients on paromomycin therapy reported either an improvement or resolution of symptoms. Four-to-six weeks posttreatment, 80% of patients initially symptomatic were free of symptoms. Four-to-six weeks posttreatment, the cure rate assessed by microbiologic response, was 92%, with only 7 treatment failures observed in the study. There was no statistically significant difference in cure rate between patients who were symptomatic and nonsymptomatic at the onset of treatment (P>0.5). Patients infected with *E histolytica* cysts had a cure rate of 93% compared to a 91% cure rate in patients with a trophozoites infection. The incidence of treatment-related side effects was low and none of the patients discontinued therapy due to adverse events. Gastrointestinal complaints were reported by 69% of patients who were initially asymptomatic, but only one patient had five or more stools per day.
Villamil et al.[15] (1964) Paromomycin 250 mg QID after meals for 12 days	OL Adults 16 TO 71 years of age with gastrointestinal symptoms and stools positive for *E histolytica*	N=35 Mean 6 months	Primary: Bacteriologic cure rate, reinfection rate, clinical response (symptomatic relief), adverse effects	Primary: After therapy with paromomycin, 97% of patients had negative stool samples for *E histolytica*. There were no amebas in the stools of 14 patients at 3-month follow-up and after 6 months of observation, the stools of 20 patients were negative for *E histolytica*. None of the patients became reinfected during the study period.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Clinical response was rated as "good" by 60%, "mild" by 25.5%, and "poor" by 14.5% of patients treated with paromomycin. There were no significant adverse effects reported in the study.
Simon et al.[16] (1967) Paromomycin 500 mg and paromomycin 250 mg for 5 days (Group A) vs paromomycin 500 mg and paromomycin 250 mg for 4 days (Group B) vs paromomycin 500 mg and paromomycin 250 mg for 3 days (Group C) vs paromomycin 500 mg and paromomycin 250 mg for 2 days (Group D)	RCT, DB Patients infected with *E histolytica*, *D fragilis* or both	N=100 Mean 66 days	Primary: Bacteriological failure rate, adverse effects	Primary: While there were no bacteriological failures in treating *E histolytica* infections in the paromomycin groups, the failure rate in the tetracycline group was 100%. While there were no bacteriological failures in treating *D fragilis* infections in groups A and B, the failure rates in the groups C, D, and the tetracycline group were 40%, 36%, and 87%, respectively. Diarrhea was the most common adverse effect, reported by 15% of patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs paromomycin 500 mg and paromomycin 250 mg for 1 day (Group E) vs tetracycline 250 mg for 10 days (Group F)				

Drug regimen abbreviations: BID=twice a day, QID=four times a day, TID=three times daily
Study abbreviations: DB=double-blind, OL=open-label, RCT=randomized controlled trial
*Diloxanide furoate not commercially available in the US.
†Aminosidine is synonymous with paromomycin.
‡Etophamide (etofamide) is a luminal amebicide, similar to diloxanide furoate, not commercially available in the US.
§Nimorazole is a 5-nitroimidazole derivative, similar to metronidazole, not commercially available in the US.

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 Amebicides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Paromomycin	capsule	N/A	N/A	$$$$

N/A=Not available

X. Conclusions

Paromomycin is approved for the treatment of amebiasis, as well as an adjunctive agent for the treatment of hepatic coma.[1-3] It is available in a generic formulation. Guidelines recommend paromomycin in combination with another antiprotozoal agent for the treatment of amebiasis to clear intestinal cysts.[4,10-11] Clinical trials have demonstrated that paromomycin is effective for the treatment of amebiasis.[12-16] For the treatment of hepatic encephalopathy, guidelines recommend lactulose as initial therapy.[17] Antibiotics are considered an alternative treatment option for acute and chronic encephalopathy.

Paromomycin is generally well tolerated and adverse events are usually limited to the gastrointestinal tract. The most common side effects observed in clinical trials were nausea, vomiting, diarrhea, abdominal cramping, and heartburn. Rare cases of eosinophilia and rash have been reported.

Therefore, all brand amebicides 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 amebicide 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antimalarials
AHFS Class 083008
May 9, 2012

I. Overview

The antimalarials are approved for the prevention and treatment of malaria.[1-9] This is a common disease worldwide and is caused by protozoan parasites of the genus *Plasmodium*, including *P. falciparum*, *P. knowlesi*, *P. malariae*, *P. ovale* and *P. vivax*. Transmission occurs after being bitten by an infected female mosquito.[13-17] Once in the systemic circulation, the parasites travel to the liver and divide/mature into schizonts (exoerythrocytic stage). After 6-16 days, the schizonts rupture and release merozoites, which invade red blood cells (erythrocytic stage).[13-17] Symptoms occur following the erythrocytic stage and include fever, chills, headache, nausea and other influenza-like symptoms. Some merozoites may differentiate into gametocytes, which can be ingested by mosquitos followed by reinfection of humans. While malaria can be treated early in the course of the disease, delays in the initiation of therapy can have serious or even fatal consequences. *P. falciparum* infections can cause rapidly progressive severe disease or death, while the non-falciparum (*P. vivax*, *P. ovale*, or *P. malariae)* species rarely cause severe complications.[19] In the United States, most cases of malaria occur among individuals who traveled to endemic regions without receiving appropriate prophylactic therapy.[13-14] The incidence of malaria has increased in recent years and drug resistance is an emerging problem.[13-17]

The antimalarials include the quinoline derivatives (chloroquine, hydroxychloroquine, quinine, mefloquine and primaquine), antifolates (atovaquone/proguanil and pyrimethamine) and artemisinin derivatives (artemether/lumefantrine).[16] The quinoline derivatives inhibit heme polymerase activity, resulting in accumulation of free heme which is toxic to the parasites.[17] The antifolates interfere with enzymes involved in folate synthesis, which is required for parasite DNA synthesis. Artemisinin derivatives bind to iron and form free radicals that are toxic to parasite proteins.[16] The majority of the antimalarials target the erythrocytic stage of malaria infection; however, some treatments also target the exoerythrocytic stage and gametocytes.

The antimalarials that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Atovaquone/proguanil, chloroquine, hydroxychloroquine, mefloquine, and primaquine are available in a generic formulation. This class was last reviewed in November 2009.

Table 1. Antimalarials Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Artemether and lumefantrine	tablet	Coartem®	none
Atovaquone and proguanil	tablet	Malarone®*	atovaquone and proguanil
Chloroquine	tablet	Aralen®*	chloroquine
Hydroxychloroquine	tablet	Plaquenil®*	hydroxychloroquine
Mefloquine	tablet	N/A	mefloquine
Primaquine	tablet	N/A	primaquine
Pyrimethamine	tablet	Daraprim®	Daraprim®
Quinine	capsule	Qualaquin®	none

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

The antimalarials 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 FDA-approved indications for the antimalarials that are noted in Table 5. 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 antimalarial 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 Antimalarials[1-9]

Organism	Artemether/ Lumefantrine	Atovaquone/ Proguanil	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Protozoa								
Plasmodium falciparum	✔	✔	✔	✔	✔	✔	✔	✔
Plasmodium malariae		✔	✔	✔			✔	
Plasmodium ovale		✔	✔	✔			✔	
Plasmodium vivax		✔	✔	✔	✔	✔	✔	
Toxoplasma gondii							✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the antimalarials are summarized in Tables 3-4.

Table 3. Treatment Guidelines Using the Antimalarials

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention (CDC): **Treatment of Malaria**[19-20] **(2011)**	Treatment – General Approach • Treatment for malaria should not be initiated until the diagnosis has been confirmed by laboratory investigations. "Presumptive treatment" without the benefit of laboratory confirmation should be reserved for extreme circumstances (strong clinical suspicion, severe disease, impossibility of obtaining prompt laboratory confirmation). • Once the diagnosis of malaria has been confirmed, appropriate antimalarial treatment must be initiated immediately. Treatment should be guided by three main factors: the infecting *Plasmodium* species, the clinical status of the patient, and the drug susceptibility of the infecting parasites as determined by the geographic area where the infection was acquired. Treatment – Uncomplicated Malaria • Refer to Table 4 for the 2011 recommendations for the treatment of uncomplicated malaria. Treatment – Severe Malaria • Patients who are considered to have manifestations of more severe disease should be treated aggressively with parenteral antimalarial therapy. • Oral antimalarial drugs (such as oral quinine, chloroquine, or mefloquine) are not recommended for the initial treatment of severe malaria. If severe malaria is strongly suspected but the first blood smear does not demonstrate parasites, a trial of parenteral antimalarial drugs should be given. • If there is clinical evidence of severe malaria, but the blood smear is reported as *P. vivax*, *P. ovale* or *P. malariae*, the patient should be treated for falciparum malaria in case of a mixed infection or misdiagnosis. • Refer to Table 4 for the 2011 recommendations for the treatment of severe malaria.
Centers for Disease Control and Prevention (CDC): **Health Information for International Travel**[21] **(2011)**	Travel to Areas with Limited Malaria Transmission • For destinations where malaria cases occur sporadically and risk for infection to travelers is assessed as being low, CDC recommends that travelers use mosquito avoidance measures only, and no chemoprophylaxis should be prescribed. Travel to Areas with Mainly *P. vivax* Malaria • For destinations where the main species of malaria present is *P. vivax*, in addition to mosquito avoidance measures, primaquine is a good choice for primary prophylaxis for travelers who are not G6PD-deficient. • For persons unable to take primaquine, other drugs can be used as described below, depending on the presence of antimalarial drug resistance. Travel to Areas with Chloroquine-Sensitive Malaria • For destinations where chloroquine-sensitive malaria is present, in addition to mosquito avoidance measures, the many effective chemoprophylaxis alternatives include chloroquine, atovaquone/proguanil, doxycycline, mefloquine, and in some instances primaquine for travelers who are not G6PD-deficient. • Longer-term travelers may prefer weekly chloroquine, while shorter-

Clinical Guideline	Recommendation(s)
	term travelers may prefer the shorter course of atovaquone/proguanil or primaquine. Travel to Areas with Chloroquine-Resistant Malaria • For destinations where chloroquine-resistant malaria is present, in addition to mosquito avoidance measures, chemoprophylaxis options are limited to atovaquone/proguanil, doxycycline, and mefloquine. Travel to Areas with Mefloquine-Resistant Malaria • For destinations where mefloquine-resistant malaria is present, in addition to mosquito avoidance measures, chemoprophylaxis options are either atovaquone/proguanil or doxycycline. Chemoprophylaxis for Infants, Children, and Adolescents • Infants of any age or weight or children and adolescents of any age can contract malaria. Therefore, all children traveling to malaria-risk areas should take an antimalarial drug. • Chloroquine and mefloquine are options for use in infants and children of all ages and weights, depending on the presence of drug resistance at their destination. • Primaquine can be used for children who are not G6PD-deficient traveling to areas with principally *P. vivax*. • Doxycycline may be used for children who are at least 8 years of age. • Atovaquone/proguanil may be used for prophylaxis for infants and children weighing at least 5 kg (11 lbs). Chemoprophylaxis during Pregnancy and Breastfeeding • Malaria infection in pregnant women can be more severe than in nonpregnant women. Malaria can increase the risk for adverse pregnancy outcomes, including prematurity, abortion, and stillbirth. For these reasons, and because no chemoprophylactic regimen is completely effective, women who are pregnant or likely to become pregnant should be advised to avoid travel to areas with malaria transmission if possible. If travel to a malarious area cannot be deferred, use of an effective chemoprophylaxis regimen is essential. • Pregnant women traveling to areas where chloroquine-resistant *P. falciparum* has not been reported may take chloroquine prophylaxis. Chloroquine has not been found to have any harmful effects on the fetus when used in the recommended doses for malaria prophylaxis; therefore, pregnancy is not a contraindication for malaria prophylaxis with chloroquine phosphate or hydroxychloroquine sulfate. • For travel to areas where chloroquine resistance is present, mefloquine is currently the only medication recommended for malaria chemoprophylaxis during pregnancy. • Because of insufficient data regarding the use during pregnancy, atovaquone/proguanil is not recommended to prevent malaria in pregnant women. • Doxycycline is contraindicated for malaria prophylaxis during pregnancy because of the risk for adverse effects seen with tetracycline, a related drug, on the fetus, which include discoloration and dysplasia of the teeth and inhibition of bone growth. • Primaquine should not be used during pregnancy because the drug may be passed transplacentally to a G6PD-deficient fetus and cause hemolytic anemia in utero. Changing Medications during Chemoprophylaxis as a Result of Adverse Effects • Medications recommended for prophylaxis against malaria have different modes of action that affect the parasites at different stages of the life cycle. Thus, if the medication needs to be changed because of

Clinical Guideline	Recommendation(s)
	side effects before a full course has been completed, there are some special considerations.
Infectious Diseases Society of America (IDSA): **The Practice of Travel Medicine[70] (2006)**	Prevention of Malaria in Travelers • Malaria is the most common preventable infectious cause of death among travelers and is the most frequent cause of fever in the returned traveler. • Most travelers who develop malaria do so because they use ineffective or no chemoprophylaxis or are not adherent to an appropriate chemoprophylactic drug regimen. • When considering antimalarial drugs, their potential adverse effects must be weighed against the risk of acquiring malaria and the traveler's access to prompt, reliable medical care. • Therapy with antimalarial drugs should be started prior to travel, and the drugs should be taken regularly during exposure and for a period of time after leaving an area in which malaria is endemic. • Travelers to the following areas should generally take an antimalarial drug: urban and rural risk areas of sub-Saharan Africa (except most of South Africa) and Oceania (including Papua [Indonesian New Guinea], Papua New Guinea, and Vanuatu), India, Bangladesh (except Dhaka), Pakistan, Nepal (Terai region), and Haiti; travelers with evening or overnight exposure in rural, non-resort areas of Southeast Asia, Central and South America, and certain parts of Mexico, North Africa, and the Dominican Republic should also take an antimalarial drug. • Chloroquine-resistant *P. falciparum* malaria is now widespread in all areas of the world in which malaria is endemic. • All travelers should be well informed about the disease and become advocates for their own care. They should understand that no antimalarial drug guarantees complete protection and that fever during or after travel (particularly in the first 2 months after travel, but as long as 6 months to 1 year after return) is a medical emergency requiring urgent assessment by a health care practitioner. Chemoprophylactic Regimens: Standard Antimalarial Drugs • Chloroquine is the drug of choice for travel to areas in which chloroquine resistance has not been described or is minimal. • For travel to areas with chloroquine-resistant *P. falciparum* (CRPF), atovaquone-proguanil, mefloquine and doxycycline are effective standard prophylactic treatments. Chemoprophylactic Regimens: Alternative Antimalarial Drugs • Primaquine has been used for decades to prevent relapses from the hypnozoite form of *P. vivax* and *P. ovale*, either during treatment of clinical cases (radical cure) or as presumptive anti-relapse therapy (terminal prophylaxis) following heavy exposure to these parasites. • Recent studies have demonstrated primaquine to be a very effective and safe chemoprophylactic 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[25] (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. • Trimethoprim-sulfamethoxazole (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.

Clinical Guideline	Recommendation(s)
	• Acute therapy for TE should be continued for at least 6 weeks, if there is clinical and radiologic improvement.
American College of Rheumatology (ACR): **Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis[23] (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 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	• Patients with rheumatoid arthritis (RA) should be established on

Clinical Guideline	Recommendation(s)
Rheumatology (BSR): **Guideline for the Management of Rheumatoid Arthritis (The First Two Years)[21]** **(2006)**	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.
American College of Rheumatology (ACR): **Guidelines for Referral and Management of Systemic Lupus Erythematosus in Adults[24]** **(1999)**	• Treatment usually consists of NSAIDs as needed, topical steroids for rash, antimalarial medications (e.g., hydroxychloroquine 200-400 mg daily), and low dose oral corticosteroids (prednisone ≤10 mg daily). • For severe life-threatening or organ-threatening disease, high dose steroids (prednisone 40-60 mg daily) may be used. • Additional treatment options that may be used depending upon severity include immunomodulators such as azathioprine, cyclophosphamide, methotrexate, chlorambucil, or cyclosporine.

Table 4. CDC Guidelines for Treatment of Malaria in the United States[20]

Clinical Diagnosis/ *Plasmodium* species	Region Infection Acquired	Recommended Drug and Adult Dose	Recommended Drug and Pediatric Dose *Pediatric dose should NEVER exceed adult dose*
Uncomplicated malaria/ *P. falciparum* or Species not identified If "species not identified" is subsequently diagnosed as *P. vivax* or *P ovale:* see *P. vivax* and *P ovale* (below) re. treatment with primaquine	**Chloroquine-resistant or unknown resistance[1]** (All malarious regions except those specified as chloroquine-sensitive listed in the box below.)	**A. Atovaquone-proguanil (Malarone®)[3]** **Adult tab = 250 mg atovaquone/ 100 mg proguanil** 4 tabs po qd x 3 days	**A. Atovaquone-proguanil (Malarone®)[3]** **Adult tab = 250 mg atovaquone/ 100 mg proguanil** **Peds tab = 62.5 mg atovaquone/ 25 mg proguanil** 5 - 8kg: 2 peds tabs po qd x 3 d 9-10kg: 3 peds tabs po qd x 3 d 11-20kg: 1adult tab po qd x 3 d 21-30kg: 2 adult tabs po qd x 3d 31-40kg: 3 adult tabs po qd x 3d >40 kg: 4 adult tabs po qd x 3d
		B. Artemether-lumefantrine (Coartem®)[3] **1 tablet = 20mg artemether and 120 mg lumefantrine** A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 dose po bid for the following 2 days. 5 - <15 kg: 1 tablet per dose 15 - <25 kg: 2 tablets per dose 25 - <35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose	
		C. Quinine sulfate plus one of the following: Doxycycline, Tetracycline, or Clindamycin **Quinine sulfate:** 542 mg base (=650 mg salt)[4] po tid x 3 or 7 days[5] **Doxycycline:** 100 mg po bid x 7 days **Tetracycline:** 250 mg po qid x 7 days **Clindamycin:** 20 mg base/kg/day po tid x 7 days	**C. Quinine sulfate[4] plus one of the following: Doxycycline[5], Tetracycline[6] or Clindamycin** **Quinine sulfate:** 8.3 mg base/kg (=10 mg salt/kg) po tid x 3 or 7 days[5] **Doxycycline:** 2.2 mg/kg po every 12 hours x 7 days **Tetracycline:** 25 mg/kg/day po divided qid x 7 days **Clindamycin:** 20 mg base/kg/day po tid x 7 days
		D. Mefloquine (Lariam® and generics)[7] 684 mg base (=750 mg salt) po as initial dose, followed by 456 mg base (=500 mg salt) po given 6-12 hours after initial dose. Total dose= 1,250 mg salt	**D. Mefloquine (Lariam® and generics)[7]** 13.7 mg base/kg (=15 mg salt/kg) po as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) po given 6-12 hours after initial dose. Total dose= 25 mg salt/kg

1 If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of their treatment regimen. Use one of the other options instead.
2 NOTE: There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum*. Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin.
3 Take with food or whole milk. If patient vomits within 30 minutes of taking a dose, then they should repeat the dose.
4 US manufactured quinine sulfate capsule is in a 324mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult due to unavailability of non-capsule forms of quinine.
5 For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.
6 Doxycycline and tetracycline are not indicated for use in children less than 8 years old. For children less than 8 years old with chloroquine-resistant *P. falciparum*, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children less than 8 years old with chloroquine-resistant *P. vivax*, mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead.
7Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia due to drug resistance.
8When treating chloroquine-sensitive infections, chloroquine and hydroxychloroquine are recommended options. However, regimens used to treat chloroquine-resistant infections may also be used if available, more convenient, or preferred.
9Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver, and thus prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in G6PD-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally one time per week for 8 weeks; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy.

Table 4. CDC Guidelines for Treatment of Malaria in the United States (Cont.)[20]

Clinical Diagnosis/ *Plasmodium* species	Region Infection Acquired	Recommended Drug and Adult Dose	Recommended Drug and Pediatric Dose *Pediatric dose should NEVER exceed adult dose*
Uncomplicated malaria/ *P. falciparum* or ***Species not identified***	**Chloroquine-sensitive** (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)	**Chloroquine phosphate (Aralen® and generics)[8]** 600 mg base (=1,000 mg salt) po immediately, followed by 300 mg base (=500 mg salt) po at 6, 24, and 48 hours Total dose: 1,500 mg base (=2,500 mg salt) **OR** **Hydroxychloroquine (Plaquenil® and generics)** 620 mg base (=800 mg salt) po immediately, followed by 310 mg base (=400 mg salt) po at 6, 24, and 48 hours Total dose: 1,550 mg base (=2,000 mg salt)	**Chloroquine phosphate (Aralen® and generics)[8]** 10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 hours Total dose: 25 mg base/kg **OR** **Hydroxychloroquine (Plaquenil® and generics)** 10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 hours Total dose: 25 mg base/kg
Uncomplicated malaria/ *P. malariae or P. knowlesi*	**All regions**	**Chloroquine phosphate:[8]** Treatment as above **OR** **Hydroxychloroquine:** Treatment as above	**Chloroquine phosphate:[8]** Treatment as above **OR** **Hydroxychloroquine:** Treatment as above
Uncomplicated malaria/ *P. vivax* or ***P. ovale***	**All regions** Note: for suspected chloroquine-resistant *P. vivax*, see row below	**Chloroquine phosphate[8] plus Primaquine phosphate[9]** **Chloroquine phosphate:** Treatment as above **Primaquine phosphate:** 30 mg base po qd x 14 days **OR** **Hydroxychloroquine plus Primaquine phosphate[9]** **Hydroxychloroquine:** Treatment as above **Primaquine phosphate:** 30 mg base po qd x 14 days	**Chloroquine phosphate plus Primaquine phosphate[9]** **Chloroquine phosphate:** Treatment as above **Primaquine:** 0.5mg base/kg po qd x 14 days **OR** **Hydroxychloroquine plus Primaquine phosphate[9]** **Hydroxychloroquine:** Treatment as above **Primaquine phosphate:** 0.5mg base/kg po qd x 14 days
Uncomplicated malaria/ *P. vivax*	**Chloroquine-resistant[10]** (Papua New Guinea and Indonesia)	**A. Quinine sulfate plus either Doxycycline or Tetracycline plus Primaquine phosphate[9]** **Quinine sulfate:** Treatment as above **Doxycycline or Tetracycline:** Treatment as above **Primaquine phosphate:** Treatment as above	**A. Quinine sulfate plus either Doxycycline[6] or Tetracycline[5] plus Primaquine phosphate[9]** **Quinine sulfate:** Treatment as above **Doxycycline or Tetracycline:** Treatment as above **Primaquine phosphate:** Treatment as above
		B. Atovaquone-proguanil plus Primaquine phosphate[9] **Atovaquone-proguanil:** Treatment as above **Primaquine phosphate:** Treatment as above	**B. Atovaquone-proguanil plus Primaquine phosphate[9]** **Atovaquone-proguanil:** Treatment as above **Primaquine phosphate:** Treatment as above
		C. Mefloquine plus Primaquine phosphate[9] **Mefloquine:** Treatment as above **Primaquine phosphate:** Treatment as above	**C. Mefloquine plus Primaquine phosphate[9]** **Mefloquine:** Treatment as above **Primaquine phosphate:** Treatment as above
Uncomplicated malaria: alternatives for pregnant women[11,12,13]	**Chloroquine-sensitive** (see uncomplicated malaria sections above for chloroquine-sensitive species by region)	**Chloroquine phosphate:** Treatment as above **OR** **Hydroxychloroquine:** Treatment as above	Not applicable
	Chloroquine resistant (see sections above for regions with chloroquine resistant ***P. falciparum and P. vivax***)	**Quinine sulfate plus Clindamycin** **Quinine sulfate:** Treatment as above **Clindamycin:** Treatment as above **OR** **Mefloquine:** Treatment as above	Not applicable

10 NOTE: There are three options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. vivax.* High treatment failure rates due to chloroquine-resistant *P. vivax* have been well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant *P. vivax* have also been documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P. vivax* regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant *P. vivax* infections, options A, B, and C are equally recommended.

11 For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.

12 Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the first trimester due to lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks.

13 For *P. vivax* and *P. ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* and *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

Table 4. CDC Guidelines for Treatment of Malaria in the United States (Cont.)[20]

Clinical Diagnosis/ *Plasmodium* species	Region Infection Acquired	Recommended Drug and Adult Dose	Recommended Drug and Pediatric Dose *Pediatric dose should NEVER exceed adult dose*
Severe malaria[14,15,16,17]	**All regions**	**Quinidine gluconate[14] plus one of the following: Doxycycline, Tetracycline, or Clindamycin** **Quinidine gluconate:** 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1-2 hrs, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 hours. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 hours, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 hours every 8 hours, starting 8 hours after the loading dose (see package insert). Once parasite density <1% and patient can take oral medication, complete treatment with oral quinine, dose as above. Quinidine/quinine course = 7 days in Southeast Asia; = 3 days in Africa or South America. **Doxycycline:** Treatment as above. If patient not able to take oral medication, give 100 mg IV every 12 hours and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. **Tetracycline:** Treatment as above **Clindamycin:** Treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hours. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. ***Investigational new drug (contact CDC for information):*** **Artesunate followed by one of the following: Atovaquone-proguanil (Malarone®), Doxycycline (Clindamycin in pregnant women), or Mefloquine**	**Quinidine gluconate[14] plus one of the following: Doxycycline[4], Tetracycline[4], or Clindamycin** **Quinidine gluconate:** Same mg/kg dosing and recommendations as for adults. **Doxycycline:** Treatment as above. If patient not able to take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg IV every 12 hours and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication. For children ≥45 kg, use same dosing as for adults. For IV use, avoid rapid administration. Treatment course = 7 days. **Tetracycline:** Treatment as above **Clindamycin:** Treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hours. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. ***Investigational new drug (contact CDC for information):*** **Artesunate followed by one of the following: Atovaquone-proguanil (Malarone®), Clindamycin, or Mefloquine**

14 Persons with a positive blood smear OR history of recent possible exposure and no other recognized pathology who have one or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of > 5%) are considered to have manifestations of more severe disease. Severe malaria is most often caused by *P. falciparum.*

15 Patients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received more than 40 mg/kg of quinine in the preceding 48 hours or if they have received mefloquine within the preceding 12 hours. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion.

16 Consider exchange transfusion if the parasite density (i.e. parasitemia) is > 10% OR if the patient has altered mental status, non-volume overload pulmonary edema, or renal complications. The parasite density can be estimated by examining a monolayer of red blood cells (RBCs) on the thin smear under oil immersion magnification. The slide should be examined where the RBCs are more or less touching (approximately 400 RBCs per field). The parasite density can then be estimated from the percentage of infected RBCs and should be monitored every 12 hours. Exchange transfusion should be continued until the parasite density is <1% (usually requires 8-10 units). IV quinidine administration should not be delayed for an exchange transfusion and can be given concurrently throughout the exchange transfusion.

17 Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the antimalarials are noted in Table 5. 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 Antimalarials[1-9]

Indication	Artemether/ Lumefantrine	Atovaquone/ Proguanil	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Prophylaxis of malaria		✔	✔	✔	✔		✔ ‡ ‡	
Radical cure (prevention of relapse) of vivax malaria						✔		
Treatment of acute malaria	✔	✔	✔	✔	✔		✔ *	✔
Treatment of extraintestinal amebiasis			✔					
Treatment of lupus erythematosus				✔ ^				
Treatment of rheumatoid arthritis				✔ ^				
Treatment of toxoplasmosis when used conjointly with a sulfonamide							✔	

*Should not be used alone to treat acute malaria. Fast-acting schizonticides such as chloroquine or quinine are indicated and preferable for the treatment of acute malaria. However, conjoint use of pyrimethamine with a sulfonamide will initiate transmission control and suppression of susceptible strains of plasmodia.
†Only when chloroquine resistance is suspected
‡Resistance to pyrimethamine is prevalent worldwide.
§Not routinely recommended; should only be considered for travelers to areas where chloroquine-resistant malaria is endemic and when alternative drugs are not available or contraindicated.
^Useful in patients who have not responded satisfactorily to drugs with less potential for serious side effects.

IV. Pharmacokinetics

The pharmacokinetic parameters of the antimalarials are listed in Table 6.

Table 6. Pharmacokinetic Parameters of the Antimalarials[1-9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Artemether and lumefantrine	A: Not reported L: Not reported	A: 95 L: 99.7	Liver	Not reported	A: 1.6-2.2 h L: 101-119 h
Atovaquone and proguanil	A: 23 P: Not reported	A: 99 P: 75	Liver	Renal (40-60)	A: 32- 84 h P: 12 -21 h
Chloroquine	89	55-60	Liver	Renal (65-70)	3-5 days
Hydroxychloroquine	Not reported	55	Liver	Renal (16-25)	32-50 days
Mefloquine	85	98	Liver	Renal (1-8)	13-30 days
Primaquine	Not reported	Not reported	Not reported	Renal (1)	4-7 hours
Pyrimethamine	Not reported	87	Not reported	Not reported	87-187 hours
Quinine	76-88	93-95	Not reported	Renal (12-30)	4-11 hours

V. Drug Interactions

Significant drug interactions with the antimalarials are listed in Table 7.

Table 7. Significant Drug Interactions with the Antimalarials[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Artemether/lumefantrine	1	Antipsychotics	The combination may increase the additive effect on the QT interval and incidence of cardiac arrhythmias.
Artemether/lumefantrine	1	Antiretroviral agents	The combination may increase lumefantrine concentrations causing QT prolongation, decreased concentration of antiretroviral resulting in loss of efficacy, or decrease in artemether/lumefantrine concentrations resulting in loss of efficacy.
Artemether/lumefantrine	1	Class IA antiarrhythmics	Prolonged QT interval and cardiac arrhythmias are a potential when class IA antiarrhythmics and artemether/lumefantrine are used concomitantly.
Artemether/lumefantrine	1	Class III antiarrhythmics	Prolonged QT interval and cardiac arrhythmias are a potential when class III antiarrhythmics and artemether/lumefantrine are used concomitantly.
Artemether/lumefantrine	1	Dronedarone	Coadministration of dronedarone and artemether/lumefantrine may increase the risk of cardiovascular toxicity, including potentially fatal

Generic Name(s)	Significance Level	Interaction	Mechanism
			cardiac arrhythmias (torsade de pointes).
Artemether/lumefantrine	1	Halofantrine	The combination of artemether/lumefantrine and halofantrine may result in an increased incidence of cardiac arrhythmias.
Artemether/lumefantrine	1	Macrolides, fluoroquinolones, triazole antifungals	Use of these agents may increase the additive effect on the QT interval and incidence of cardiac arrhythmias.
Artemether/lumefantrine	1	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and artemether/lumefantrine.
Artemether/lumefantrine	1	Nonsedating antihistamines	Use of artemether/lumefantrine and astemizole/terfenadine may increase the additive effect on the QT interval and incidence of cardiac arrhythmias.
Artemether/lumefantrine	1	Tetrabenazine	Additive QT prolongation may occur during coadministration of tetrabenazine and artemether/lumefantrine.
Artemether/lumefantrine	1	Toremifene	Prolonged QT interval and cardiac arrhythmias are a potential when toremifene and artemether/lumefantrine are used concomitantly.
Artemether/lumefantrine	1	Vandetanib	Prolonged QT interval and cardiac arrhythmias are a potential when vandetanib and artemether/lumefantrine are used concomitantly.
Artemether/lumefantrine	1	Vemurafenib	Prolonged QT interval and cardiac arrhythmias are a potential when vemurafenib and artemether/lumefantrine are used concomitantly.
Atovaquone/proguanil	1	Anticoagulants	Proguanil may inhibit the hepatically synthesized clotting factors resulting in potentiation of anticoagulation.
Chloroquine	1	Class IA and III antiarrhythmics	Prolonged QT interval and cardiac arrhythmias are a potential when antiarrhythmics and chloroquine are used concomitantly.
Chloroquine	1	H_1 antagonists	Use of chloroquine and H_1 antagonists may increase the risk of cardiovascular toxicity, including potentially fatal cardiac arrhythmias (torsade de pointes).
Chloroquine	1	Macrolides, ketolides and fluoroquinolones	Cardiac arrhythmias resulting from the potential for additive

Generic Name(s)	Significance Level	Interaction	Mechanism
			QT prolongation should be considered as a possibility when these agents are coadministered.
Chloroquine	1	Mefloquine	Convulsions are a potential when mefloquine and chloroquine are used concomitantly.
Chloroquine	1	Methadone	Coadministration of methadone and chloroquine may cause significant prolongation of the cardiac QT interval, and possibly lead to torsades de pointes arrhythmias, especially in high doses, female sex, hypokalemia, or patients with a history of cardiac conduction disease.
Chloroquine	1	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and chloroquine.
Hydroxychloroquine	1	Mefloquine	The combination of hydroxychloroquine and mefloquine may result in an increased risk of cardiac arrhythmias due to prolonged QT intervals.
Hydroxychloroquine	1	Natalizumab	Hydroxychloroquine may increase the plasma concentration and toxicity of natalizumab resulting in an increased occurrence of concurrent infection.
Mefloquine	1	Antipsychotics	The combination of mefloquine and quetiapine/ziprasidone may result in an increased risk of cardiac arrhythmias due to prolonged QT intervals.
Mefloquine	1	Dronedarone	Coadministration of dronedarone and mefloquine may increase the risk of cardiovascular toxicity, including potentially fatal cardiac arrhythmias (torsade de pointes).
Mefloquine	1	Halofantrine	The combination of mefloquine and halofantrine may result in an increased incidence of cardiac arrhythmias.
Mefloquine	1	Ketoconazole	The combination of mefloquine or within 15 weeks of the last dose of mefloquine and ketoconazole may result in an increased incidence of cardiac arrhythmias.
Mefloquine	1	Quinidine or quinine	Prolonged QT interval and convulsions are a potential when

Generic Name(s)	Significance Level	Interaction	Mechanism
			mefloquine and quinidine/quinine are used concomitantly.
Mefloquine	1	Tetrabenazine	Additive QT prolongation may occur during coadministration of tetrabenazine and mefloquine.
Mefloquine	1	Toremifene	Prolonged QT interval and cardiac arrhythmias are a potential when toremifene and mefloquine are used concomitantly.
Mefloquine	1	Vandetanib	Prolonged QT interval and cardiac arrhythmias are a potential when vandetanib and mefloquine are used concomitantly.
Mefloquine	1	Vemurafenib	Prolonged QT interval and cardiac arrhythmias are a potential when vemurafenib and mefloquine are used concomitantly.
Primaquine	1	Mefloquine	Prolonged QT interval and convulsions are a potential when mefloquine and primaquine are used concomitantly.
Pyrimethamine	1	Methotrexate	Coadministration of pyrimethamine and methotrexate may increase the risk of bone marrow suppression.
Pyrimethamine	1	Sulfonamides	Coadministration of pyrimethamine and sulfonamides or trimethoprim-sulfamethoxazole may increase the risk of bone marrow suppression.
Pyrimethamine	1	Zidovudine	Coadministration of pyrimethamine and zidovudine may increase the risk of bone marrow suppression.
Quinine	1	Anticoagulants	Quinine derivatives may inhibit the hepatically synthesized clotting factors resulting in potentiation of anticoagulation and possible hemorrhage.
Quinine	1	Astemizole	Quinine may inhibit the metabolism of astemizole and result in torsades de pointes.
Quinine	1	Class IA and III antiarrhythmics	Coadministration of quinine with other antiarrhythmic agents may result in QT prolongation.
Quinine	1	Halofantrine	The combination of quinine and halofantrine may result in an increased incidence of cardiac arrhythmias.
Quinine	1	Macrolides	Coadministration of macrolides and quinine may increase the

Generic Name(s)	Significance Level	Interaction	Mechanism
			serum concentration of quinine.
Quinine	1	Mefloquine	The combination of quinine and mefloquine may result in an increased incidence of cardiac arrhythmias.
Quinine	1	Nondepolarizing muscle relaxants	The neuromuscular blocking effects of non-depolarizing muscle relaxants may be increased. Prolonged respiratory depression with extended periods of apnea may occur.
Quinine	1	Rifamycins	Rifamycins increase the hepatic metabolism of quinine may result in reduced therapeutic effects of quinine.
Artemether/lumefantrine	2	Dapsone	Dapsone may increase the risk of hemolytic reactions; closely monitor patients who are taking dapsone and artemether/lumefantrine, particularly patients deficient in glucose-6-phosphate dehydrogenase (G6PD), methemoglobin reductase, or with hemoglobin M.
Artemether/lumefantrine	2	Hormonal contraceptives	Serum concentrations of hormonal contraceptives may be decreased by artemether
Atovaquone/proguanil	2	Etoposide	Plasma concentrations of etoposide may be increased by atovaquone.
Atovaquone/proguanil	2	Rifamycins	Plasma concentrations of atovaquone may be decreased by rifamycins.
Atovaquone/proguanil	2	Tetracyclines	Tetracyclines may decrease the plasma concentrations and pharmacologic effects of atovaquone.
Chloroquine	2	Antacids	Coadministration of chloroquine and antacids can reduce the absorption and efficacy of chloroquine.
Chloroquine	2	Cyclosporine	Chloroquine may increase the plasma concentration and toxicity of cyclosporine.
Chloroquine	2	Dapsone	Dapsone may increase the risk of hemolytic reactions; closely monitor patients who are taking dapsone and chloroquine, particularly patients deficient in glucose-6-phosphate dehydrogenase (G6PD), methemoglobin reductase, or with hemoglobin M.
Chloroquine	2	Flecainide	Additive QT prolongation may occur during coadministration of

Generic Name(s)	Significance Level	Interaction	Mechanism
			flecainide and chloroquine.
Chloroquine	2	Perflutren	Additive QT prolongation may occur during coadministration of perflutren and chloroquine.
Chloroquine	2	Propafenone	Additive QT prolongation may occur during coadministration of propafenone and chloroquine.
Chloroquine	2	Tetrabenazine	Additive QT prolongation may occur during coadministration of tetrabenazine and chloroquine.
Hydroxychloroquine	2	Dapsone	Dapsone may increase the risk of hemolytic reactions; closely monitor patients who are taking dapsone and hydroxychloroquine, particularly patients deficient in glucose-6-phosphate dehydrogenase (G6PD), methemoglobin reductase, or with hemoglobin M.
Hydroxychloroquine	2	Digoxin	Hydroxychloroquine appears to decrease the biliary clearance of digoxin resulting in increased digoxin serum levels with possible toxicity.
Hydroxychloroquine	2	Leflunomide	Pancytopenia, agranulocytosis, and/or thrombocytopenia may occur during coadministration of hydroxychloroquine and leflunomide.
Hydroxychloroquine	2	Roflumilast	Coadministration of hydroxychloroquine and roflumilast may enhance immunosuppression.
Mefloquine	2	Anticonvulsants	Coadministration of mefloquine and anticonvulsants may reduce seizure control by lowering the plasma levels of anticonvulsants.
Mefloquine	2	Beta-adrenergic blockers	Coadministration of mefloquine and beta-adrenergic blockers may cause cardiovascular toxicity, including electrocardiographic abnormalities such as QT interval prolongation.
Primaquine	2	Dapsone	Dapsone may increase the risk of hemolytic reactions; closely monitor patients who are taking dapsone and primaquine, particularly patients deficient in glucose-6-phosphate dehydrogenase (G6PD), methemoglobin reductase, or with hemoglobin M.
Pyrimethamine	2	Dapsone	Dapsone may increase the risk of hemolytic reactions; closely

Generic Name(s)	Significance Level	Interaction	Mechanism
			monitor patients who are taking dapsone and pyrimethamine, particularly patients deficient in glucose-6-phosphate dehydrogenase (G6PD), methemoglobin reductase, or with hemoglobin M.
Quinine	2	Anticholinesterases	The beneficial effects of anticholinesterases in the treatment of myasthenia gravis may be reversed by quinine.
Quinine	2	Digoxin	Quinine appears to decrease the biliary clearance of digoxin resulting in increased digoxin serum levels with possible toxicity.
Quinine	2	Succinylcholine	Quinine may produce a decrease in plasma cholinesterase activity resulting in a slowed metabolic rate for succinylcholine. This may result in prolongation of the neuromuscular blockade produced by succinylcholine.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the antimalarials are listed in Table 8. The boxed warnings for the antimalarials are listed in Tables 9-10.

Table 8. Adverse Drug Events (%) Reported with the Antimalarials[1-9]

Adverse Events	Artemether/ Lumefantrine	Atovaquone/ Proguanil	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Cardiovascular								
Arrhythmia	-	-	-	-	-	✔	✔	✔
Atrial fibrillation	-	-	-	-	-	-	-	✔
Atrioventricular block	-	-	-	-	-	-	-	✔
Bradycardia	-	-	-	-	<1	-	-	✔
Cardiac arrest	-	-	-	-	-	-	-	✔
Cardiomyopathy	-	-	✔	✔	-	-	-	-
Chest pain	-	-	-	-	✔	-	-	✔
Electrocardiogram changes	-	-	✔	-	✔	-	-	✔
Flushing	-	-	-	-	✔	-	-	✔
Hypotension	-	-	✔	-	✔	-	-	✔
Hypertension	-	-	-	-	✔	-	-	-
Palpitations	18	-	-	-	✔	-	-	✔
Syncope	-	-	-	-	✔	-	-	✔
Tachycardia	-	-	-	-	✔	-	-	✔
Torsades de pointes	-	-	-	-	-	-	-	✔
Central Nervous System								
Agitation	<3	-	✔	-	✔	-	-	-
Altered mental status	-	-	-	-	-	-	-	✔
Aphasia	-	-	-	-	-	-	-	✔
Asthenia	5-38	-	-	-	<1	-	-	✔
Ataxia	<3	-	-	✔	-	-	-	✔
Clonus	<3	-	-	-	-	-	-	-
Coma	-	-	-	-	-	-	-	✔
Confusion	-	-	-	-	✔	-	-	✔
Convulsions	-	-	-	-	✔	-	-	-
Delirium	-	-	✔	-	-	-	-	-
Depression	-	-	✔	-	✔	-	-	-
Dizziness	4-39	5	-	✔	✔	-	✔	✔
Dystonic reaction	-	-	-	-	-	-	-	✔
Fine motor delay	<3	-	-	-	-	-	-	-
Gait disturbance	<3	-	-	-	-	-	-	-

Adverse Events	Artemether/ Lumefantrine	Atovaquone/ Proguanil	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Fatigue	3-17	-	-	-	1-10	-	-	-
Fever	25-29	-	-	-	1-10	-	-	✔
Headache	13-56	10	✔	✔	1-10	✔	-	✔
Hyperreflexia	<3	-	-	-	-	-	-	-
Hypoesthesia	<3	-	-	-	-	-	-	-
Insomnia	5	-	✔	-	✔	-	✔	-
Irritability	-	-	-	✔	-	-	-	-
Lightheadedness	-	-	-	-	-	-	✔	-
Malaise	3	-	-	-	-	-	✔	-
Mood swings	<3	-	-	-	✔	-	-	-
Nervousness	-	-	-	✔	-	-	-	-
Nightmares	-	-	-	✔	-	-	-	-
Nystagmus	<3	-	-	-	-	-	-	-
Personality changes	-	-	✔	✔	<1	-	-	-
Psychosis	-	-	✔	✔	-	-	-	-
Restlessness	-	-	-	-	✔	-	-	✔
Seizures	-	-	✔	✔	<1	-	-	✔
Sleep disorder	22	-	-	-	-	-	-	-
Somnolence	-	-	-	-	✔	-	-	-
Syncope	-	-	-	-	✔	-	-	-
Tremor	<3	-	-	-	-	-	-	-
Vertigo	3	-	-	✔	✔	-	-	✔
Dermatological								
Acrodermatitis	<3	-	-	-	-	-	-	-
Allergic skin reactions	-	-	-	-	-	-	-	✔
Angioedema	-	-	-	✔	-	-	-	-
Dermatitis	-	-	-	-	-	-	✔	-
Edema	-	-	-	-	✔	-	-	-
Erythema multiforme	-	✔	-	-	✔	-	✔	✔
Exfoliative dermatitis	-	-	-	✔	✔	-	-	✔
Hair loss	-	-	✔	✔	<1	-	-	-
Impetigo	<3	-	-	-	-	-	-	-
Micropapular eruptions	-	-	-	✔	-	-	-	✔
Photosensitivity	-	-	✔	-	-	-	-	✔
Pigmentation	-	-	✔	✔	-	-	✔	-
Pruritus	4	1-6	✔	✔	<1	✔	-	✔
Rash	3	-	-	-	1-10	-	✔	✔

Adverse Events	Artemether/ Lumefantrine	Atovaquone/ Proguanil	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Skin and hair bleaching	-	-	✔	✔	-	-	-	-
Stevens-Johnson syndrome	-	✔	-	✔	✔	-	✔	✔
Sweating	-	-	-	-	✔	-	-	✔
Toxic epidermal necrosis	-	-	-	-	-	-	✔	✔
Urticaria	<3	-	-	✔	-	-	-	✔
Endocrine and Metabolic								
Cholestatic jaundice	-	-	-	-	-	-	-	✔
Elevated liver enzyme levels	-	-	-	-	-	-	-	✔
Hepatitis	-	-	-	-	-	-	-	✔
Hypersensitivity reactions	-	-	-	-	-	-	✔	✔
Hypoglycemia	-	-	-	-	-	-	-	✔
Gastrointestinal		-						
Abdominal cramps/pain	8-17	17	✔	✔	1-10	✔	✔	✔
Abnormal liver function	-	-	-	✔	-	-	-	✔
Anorexia	13-40	5	✔	✔	✔	-	✔	✔
Atopic glossitis	-	-	-	-	-	-	✔	-
Constipation	<3	-	-	-	-	-	-	-
Diarrhea	7-8	8	✔	✔	1-10	-	✔	✔
Dyspepsia	<3	-	-	-	-	✔	-	-
Dysphagia	<3	-	-	-	-	-	-	-
Epigastric distress	-	-	-	-	-	✔	-	-
Gastroenteritis	<3	-	-	-	-	-	-	-
Hepatic failure	-	-	-	✔	-	-	-	-
Nausea	5-26	12	✔	✔	1-10	✔	-	✔
Peptic ulcer	<3	-	-	-	-	-	-	-
Vomiting	17-18	12	✔	✔	3	✔	✔	✔
Weight loss	-	-	-	✔	-	-	-	-
Genitourinary								
Hematuria	<3	-	-	-	-	-	✔	-
Proteinuria	<3	-	-	-	-	-	-	-
Renal failure	-	-	-	-	-	-	-	✔
Renal impairment	-	-	-	-	-	-	-	✔
Urinary tract infection	<3	-	-	-	-	-	-	-
Hematologic								
Agranulocytosis	-	-	✔	✔	-	✔	-	✔
Anemia	4-9	✔	-	✔	-	✔	-	-
Aplastic anemia	-	-	✔	✔	-	-	-	✔

Adverse Events	Artemether/ Lumefantrine	Atovaquone/ Proguanil	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Coagulopathy	-	-	-	-	-	-	-	✔
Eosinophilia	<3	-	-	-	-	-	✔	-
Hematocrit decreased	<3	-	-	-	✔	-	-	-
Hemolytic anemia	-	-	-	-	-	✔	-	✔
Leukocytosis	<3	-	-	-	-	✔	-	-
Leukopenia	<3	-	-	✔	✔	✔	✔	-
Lymphocyte morphology abnormal	<3	-	-	-	-	-	-	-
Megaloblastic anemia	-	-	-	-	-	-	✔	-
Methemoglobinemia	-	-	-	-	-	✔	-	-
Neutropenia	-	✔	✔	-	-	-	-	✔
Pancytopenia	-	✔	✔	-	-	-	✔	✔
Thrombocytopenia	<3	-	✔	✔	✔	-	-	✔
Thrombocytosis	<3	-	-	-	-	-	-	-
Hepatic								
Hepatitis	-	✔	-	-	-	-	-	-
Hepatomegaly	6-9	-	-	-	-	-	-	-
Laboratory Test Abnormalities								
ALT increased	<3	-	✔	-	-	-	-	-
AST increased	4	-	✔	-	-	-	-	-
Hypokalemia	<3	-	-	-	-	-	-	-
Hypoprothrombinemia	-	-	-	-	-	-	-	✔
Transaminases elevated	-	-	-	-	✔	-	-	-
Musculoskeletal								
Asthenia	-	✔	-	-	-	-	-	-
Atrophy	-	-	✔	✔	-	-	-	-
Arthralgia	3-34	-	-	-	✔	-	-	-
Back pain	<3	-	-	-	-	-	-	-
Muscle cramps	-	-	-	-	✔	-	-	-
Myalgia	3-32	-	-	-	1-10	-	-	✔
Myopathy	-	-	✔	✔	-	-	-	-
Reflex depression	-	-	✔	✔	-	-	-	-
Sensory changes	-	-	✔	✔	-	-	-	-
Weakness	-	-	✔	-	✔	-	-	✔
Respiratory								
Asthma	<3	-	-	-	-	-	-	✔
Bronchospasm	-	-	-	✔	-	-	-	-
Cough	6-23	-	-	-	-	-	-	-

Adverse Events	Artemether/ Lumefantrine	Atovaquone/ Proguanil	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Dyspnea	-	-	-	-	✔	-	-	✔
Influenza	<3	-	-	-	-	-	-	-
Nasopharyngitis	≤3	-	-	-	-	-	-	-
Pneumonia	<3	-	-	-	-	-	-	-
Pulmonary edema	-	-	-	-	-	-	-	✔
Respiratory tract infection	<3	-	-	-	-	-	-	-
Rhinitis	4	-	-	-	-	-	-	-
Other								
Abnormal color vision	-	-	-	✔	-	-	-	✔
Abscess	<3	-	-	-	-	-	-	-
Anaphylaxis	-	✔	-	-	-	✔	-	-
Angioedema	✔	-	-	-	-	-	-	-
Blindness	-	-	-	-	-	-	-	✔
Blurred vision	-	-	✔	✔	-	-	-	✔
Changes in accommodation	-	-	✔	✔	-	✔	-	✔
Chills	5-23	-	-	-	1-10	-	-	✔
Conjunctivitis	<3	-	-	-	-	-	-	-
Corneal deposits	-	-	-	✔	-	-	-	-
Deafness/hearing impairment	-	-	✔	✔	✔	-	-	✔
Diplopia	-	-	-	-	-	-	-	✔
Ear infection	<3	-	-	-	-	-	-	-
Helminthic infection	<3	-	-	-	-	-	-	-
Hookworm infection	<3	-	-	-	-	-	-	-
Hypersensitivity reactions	✔	✔	-	-	-	-	-	-
Lupus-like syndrome	-	-	-	-	-	-	-	✔
Ocular edema	-	-	-	✔	-	-	-	-
Oral herpes	<3	-	-	-	-	-	-	-
Photophobia	-	-	-	✔	-	-	-	-
Retinopathy	-	-	✔	✔	-	-	-	-
Scotomas	-	-	✔	✔	-	-	-	✔
Splenomegaly	9	-	-	-	-	-	-	-
Suicide	-	-	-	-	-	-	-	✔
Tinnitus	<3	-	✔	✔	✔	-	-	✔

✔ Percent not specified
\- Event not reported

Table 9. Boxed Warning for Chloroquine, Hydroxychloroquine and Primaquine[1]

WARNING
Physicians should completely familiarize themselves with the complete contents of the monograph before prescribing chloroquine, hydroxychloroquine, and primaquine.

Table 10. Boxed Warning for Quinine[1]

WARNING
Quinine use for the treatment or prevention of nocturnal leg cramps may result in serious and life-threatening hematologic reactions, including thrombocytopenia and hemolytic uremic syndrome/thrombotic thrombocytopenic purpura. Chronic renal impairment associated with the development of thrombotic thrombocytopenic purpura has been reported. The risk associated with quinine use in the absence of evidence of its effectiveness in the treatment or prevention of nocturnal leg cramps outweighs any potential benefit.

VII. Dosing and Administration

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

Table 11. Usual Dosing Regimens for the Antimalarials[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Artemether and lumefantrine	Treatment of Acute Malaria: 4 tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice daily for the following two days	Treatment of Acute Malaria: 5 kg to <15 kg: 1 tablet as an initial dose, 1 tablet again after 8 hours, and then 1 tablet twice daily for the following two days 15 kg to <25 kg: 2 tablets as an initial dose, 2 tablets again after 8 hours, and then 2 tablets twice daily for the following two days 25 kg to <35 kg: 3 tablets as an initial dose, 3 tablets again after 8 hours, and then 3 tablets twice daily for the following two days ≥35 kg: 4 tablets as an initial dose, 4 tablets again after 8 hours, and then 4 tablets twice daily for the following two days	Tablet: 20-120 mg
Atovaquone and proguanil	Prophylaxis of Malaria: 250mg/100 mg once daily. Begin 1-2 days before entering an endemic area and continue daily during stay and for 7 days after return. Treatment of Acute Malaria: 4 tablets (total daily dose 1 g atovaquone/400 mg proguanil) as a single dose	Prophylaxis of Malaria: 11-20 kg: 62.5 mg/25 mg daily 21-30 kg: 125 mg/50 mg daily as a single dose 31-40 kg: 187.5 mg/75 mg daily as a single dose >40 kg: 250 mg/100 mg daily Begin 1-2 days before entering an endemic area and	Tablet: 62.5-25 mg 250-100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	daily for 3 consecutive days	continue daily during stay and for 7 days after return. Treatment of Acute Malaria: 5-8 kg: 125 mg/50 mg daily for 3 consecutive days 9-10 kg: 187.5 mg/75 mg daily for 3 consecutive days 11-20 kg: 250 mg/100 mg daily for 3 consecutive days 21-30 kg: 500 mg/200 mg daily for 3 consecutive days 31-40 kg: 750 mg/300 mg daily for 3 consecutive days >40 kg: 1,000 mg/400 mg daily for 3 consecutive days	
Chloroquine	Extraintestinal Amebiasis: 1 g (600 mg base) daily for 2 days, followed by 500 mg (300 mg base) daily for at least 2-3 weeks. Treatment is usually combined with an effective amebicide. Prophylaxis of Malaria: 500 mg (300 mg base) on the same day each week. Begin 2 weeks prior to exposure; if therapy cannot begin 2 weeks before exposure, an initial loading dose of 1 g (600 mg base) should be given in two divided doses, six hours apart. Continue for 8 weeks after leaving endemic area. Treatment of Acute Malaria: 1 g (600 mg base), followed by an additional 500 mg (300 mg base) after 6 to 8 hours, and a single dose of 500 mg (300 mg base) on each of two consecutive days	Prophylaxis of Malaria: 5mg/kg (calculated as base) on the same day each week. Begin 2 weeks prior to exposure; if therapy cannot begin 2 weeks before exposure, an initial loading dose of 10 mg/kg (calculated as base) should be given in two divided doses, six hours apart. Continue for 8 weeks after leaving endemic area. Treatment of Acute Malaria: First dose: 10 mg/kg (calculated as base but not to exceed 600 mg base) Second dose: 5 mg/kg (calculated as base but not to exceed 300 mg base) given 6 hours after first dose Third dose: 5 mg/kg (calculated as base) given 24 hours after first dose Fourth dose: 5 mg/kg (calculated as base) given 36 hours after first dose	Tablet: 250 mg 500 mg
Hydroxychloroquine	Lupus Erythematosus: Initial, 400 mg once or twice daily continued for several weeks or months; maintenance: 200-400 mg daily Prophylaxis of Malaria: 400 mg (310 mg base) weekly on the exact same day. Begin 2 weeks prior to exposure; if therapy cannot begin 2 weeks before	Prophylaxis of Malaria: 5 mg base/kg (calculated as base) weekly on the exact same day. Begin 2 weeks prior to exposure; if therapy cannot begin 2 weeks before exposure, an initial loading dose of 10 mg/kg (calculated as base) should be given in two divided doses, six hours apart. Continue for 8 weeks after leaving endemic area.	Tablet: 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	exposure, an initial loading dose of 800 mg (620 mg base) should be given in two divided doses, six hours apart. Continue for 8 weeks after leaving endemic area. Rheumatoid Arthritis: Initial, 400 mg to 600 mg daily; maintenance: 200 mg to 400 mg daily Treatment of Acute Malaria: 800 mg (620 mg base) initially, followed by 400 mg (310 mg base) in 6 to 8 hours and 400 mg (310 mg base) on each of two consecutive days. An alternative method, employing a single dose of 800 mg (620 mg base) has also proved effective.	Treatment of Acute Malaria: First dose: 10 mg/kg (calculated as base but not to exceed 620 mg base) Second dose: 5 mg/kg (calculated as base but not to exceed 310 mg base) 6 hours after first dose Third dose: 5 mg/kg (calculated as base but not to exceed 310 mg base) 18 hours after second dose Fourth dose: 5 mg/kg (calculated as base but not to exceed 310 mg base) 24 hours after third dose	
Mefloquine	Prophylaxis of Malaria: 250 mg once weekly. Begin 1 week before arrival in an endemic area and continue for 4 additional weeks after leaving endemic area. Treatment of Acute Malaria: 1,250 mg given as a single dose	Prophylaxis of Malaria: ≥6 months of age: 20-30 kg: ½ tablet once weekly 30-45 kg: ¾ tablet once weekly >40 kg: 1 tablet once weekly Begin 1 week before arrival in an endemic area and continue for 4 additional weeks after leaving endemic area. Treatment of Acute Malaria: ≥6 months of age: 20-25 mg/kg, which may be split into two doses separated by 6-8 hours	Tablet: 250 mg
Primaquine	Radical Cure of Vivax Malaria, Prevention of Relapse of Vivax Malaria, Following Termination of Chloroquine Suppressive Therapy: 1 tablet (15 mg base) daily for 14 days	Safety and efficacy in children have not been established.	Tablet: 26.3 mg
Pyrimethamine	Prophylaxis of Malaria: 25 mg once weekly Treatment of Acute Malaria: 25 mg daily for 2 days in combination with a sulfonamide. If used alone,	Prophylaxis of Malaria: <4 years of age: 6.25 mg once weekly 4-10 years of age: 12.5 mg once weekly >10 years of age: 25 mg once weekly	Tablet: 25 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	use 50 mg daily for 2 days Treatment of Toxoplasmosis: Initial: 50-75 mg daily (with 1-4 grams of sulfadoxine) for 1-3 weeks, then reduce dose by half and continue for and additional 4-5 weeks	Treatment of Acute Malaria: 4-10 years of age: 25 mg daily for 2 days in combination with a sulfonamide Treatment of Toxoplasmosis: 1 mg/kg divided into 2 daily doses; after 2-4 days, may reduce dose by half and continue for 1 month.	
Quinine	Treatment of Acute Malaria: 648 mg every 8 hours for 7 days	Treatment of Acute Malaria: ≥16 years of age: 648 mg every 8 hours for 7 days	Capsule: 324 mg

VIII. Effectiveness

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

Table 12. Comparative Clinical Trials with the Antimalarials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Prophylaxis of Malaria				
Overbosch et al.[31] (2001) Atovaquone-proguanil vs mefloquine	DB, MC, RCT Nonimmune patients who traveled to malaria-endemic areas for up to 28 days	N=966 60 days following return from endemic area	Primary: Frequency of adverse events Secondary: Frequency of treatment-limiting adverse events, efficacy of prophylaxis	Primary: At least 1 adverse event was reported in 352 (71.4%) of 493 subjects in the atovaquone-proguanil group and 325 (67.3%) of 483 subjects in the mefloquine group 7 days after returning from a malaria-endemic area (4.1% difference; 95% CI: –1.7 to 9.9). The total number of adverse events reported was 1,037 (38.4 per 100 person-weeks) in the atovaquone-proguanil group and 1,163 (43.4 per 100 person weeks) in the mefloquine group. Adverse events were reported in 318 (64.5%) of 493 subjects who received atovaquone-proguanil and 324 (67.1%) of 483 subjects who received mefloquine (-2.6% difference; 95% CI: –8.5 to 3.4). Of the 2,120 treatment-associated adverse events, 1,310 (62%) were considered to be unrelated to the study drug. Treatment-associated adverse events occurred in a significantly higher proportion of subjects on mefloquine compared with those on atovaquone-proguanil (42% vs 30%; P=0.01). Adverse events associated with the study drug were described as moderate or severe in 51 (10%) of 493 subjects (96 events) who received atovaquone-proguanil and in 92 (19%) of 483 subjects (194 events) who received mefloquine (difference 9%; P=0.01). These events were severe in 19 subjects (4%; 31 events) who received atovaquone-proguanil and in 29 subjects (6%; 55 events) who received mefloquine. Secondary: More patients in the mefloquine group discontinued treatment due to adverse effects compared to the atovaquone-proguanil group (26 subjects vs 16 subjects). The event was attributed to treatment in 37 subjects. Twenty-eight events occurred in 13 subjects in the atovaquone-proguanil arm, and 79 events occurred in 24 subjects in the mefloquine arm.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Four subjects were evaluated for malaria, but serologic testing indicated that none had malaria. A total of 963 subjects completed the 60-day follow-up period.
Høgh et al.[32] (2000) Atovaquone-proguanil vs chloroquine and proguanil	DB, PC, RCT Patients planning to travel for up to 28 days to a *P falciparum*-endemic area	N=1,008 60 days after leaving a malaria-endemic area	Primary: Overall frequency of adverse events assessed at 7 days and 28 days after leaving the malaria-endemic area Secondary: Frequency of treatment-limiting adverse events	Primary: At least one adverse event was reported by 311 of 511 (61%) participants in the atovaquone-proguanil group and 329 of 511 (64%) in the chloroquine-proguanil group at 7 days after return from a malaria-endemic area (-3.5% difference; 95% CI: –9.5% to 2.4%). Adverse events not attributable to placebo were reported by 296 of 511 (58%) of those receiving atovaquone-proguanil and 329 of 511 (64%) receiving chloroquine-proguanil (–6.5%, 95% CI: –12·4% to –0.5%). Adverse events attributed to study drug occurred in more participants in the chloroquine-proguanil arm than in the atovaquone-proguanil arm (28% vs 22%, P=0.024). Moderate-to-severe adverse events attributable to the study drug occurred in 37 (7%) participants (54 events) receiving atovaquone-proguanil and 56 (11%) (97 events) on chloroquine-proguanil experienced (difference=4%, P=0.05). Secondary: Eleven people in the atovaquone-proguanil arm and 16 in the chloroquine-proguanil arm discontinued study drug prematurely because of adverse events. Study drugs were not thought to be associated with any serious adverse events.
Camus et al.[33] (2004) Atovaquone-proguanil vs chloroquine and proguanil	MC, OL, RCT Nonimmune pediatric travelers (ages 2–17 years) to areas where there was a substantial risk of acquiring *P falciparum* infection	N=221 60 days after travel	Primary: Frequency of adverse events (during travel plus 7 days after and while subjects were receiving study drug)	Primary: No serious adverse events or deaths occurred in the study. A similar proportion of subjects in each treatment group (35% and 37% of atovaquone-proguanil and chloroquine-proguanil recipients, respectively) reported adverse events during travel and 7 days after returning (–0.015; 95% CI: –0.14 to 0.11). There was a lower incidence of abdominal pain and vomiting in the atovaquone-proguanil group than in the chloroquine-proguanil group (6%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				vs 13% for both events; between-group difference in proportions, –0.062; 95% CI: –0.14 to 0.01). Thirty-five percent of subjects in the atovaquone-proguanil group reported experiencing at least 1 adverse event compared with 41% of subjects in the chloroquine-proguanil group (between-group difference in proportions, –0.060; 95% CI: –0.19 to 0.07). There was a similar frequency of adverse events between the atovaquone-proguanil group through day 7 after travel (7% vs 8%, respectively, between-group difference in proportions, –0.008; 95% CI: –0.08 to 0.06). Throughout treatment, a lower proportion of atovaquone-proguanil recipients experienced drug-related adverse events (8% vs 14%; between-group difference in proportions, –0.062; 95% CI: –0.15 to 0.02). This difference was primarily the result of a greater number of chloroquine-proguanil recipients with digestive tract complaints (10% vs 5%; between-group difference in proportions, –0.045; 95% CI: –0.11 to 0.03).
Shanks et al.[55] (1998) Atovaquone-proguanil 250 mg/100 mg daily vs atovaquone-proguanil 500 mg/200 mg daily vs placebo	DB, PC, RCT Adult volunteers in a highly malarious area of western Kenya where chloroquine resistance is widespread	N=198 10 weeks	Primary: Development of parasitemia confirmed by blood smear during prophylaxis, symptoms were also tracked Secondary: Adverse events	Primary: All patients in the low-dose and high-dose atovaquone-proguanil groups remained malaria-free during the 10-week prophylaxis period, compared to only 48% in the placebo group (P<0.001). Secondary: Both atovaquone-proguanil prophylactic treatments were well tolerated when compared to placebo. The most commonly reported adverse events were dyspepsia and gastritis, which occurred with a frequency of 6% to 12% and 7% to 9%, respectively, in the atovaquone-proguanil treatment groups and 13% and 7%, respectively, in the placebo group.
Sukwa et al.[56] (1999)	DB, PC, RCT Adult volunteers in	N=274 10 weeks	Primary: Development of parasitemia, as	Primary: The prophylaxis success rates in the atovaquone-proguanil and placebo groups were 98% and 63%, respectively (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atovaquone-proguanil 250 mg/100 mg daily vs placebo	a highly malarious area of Zambia		confirmed by blood smear Secondary: Adverse events	Secondary: The most commonly reported adverse events were headache (4% treatment group compared to 9% placebo) and abdominal pain (3% treatment group compared to 5% placebo).
Lell et al.[57] (1998) Atovaquone-proguanil (weight-based dosing) daily vs placebo	DB, PC, RCT Gabonese children 4-16 years old who lived in a hyperendemic area for chloroquine-resistant *P falciparum* malaria	N=320 12 weeks + 4 weeks of medication-free follow-up	Primary: Positive blood smear, adverse events	Primary: After 12 weeks, a positive blood smear was identified in 25 children in the placebo group and none of the children in the atovaquone-proguanil group (P<0.001). During follow-up weeks 12 to 14, during which the children did not receive medication, positive blood smears were found in 6 placebo-group children and in none of the children on atovaquone plus proguanil (P=0.012). At week 16, the group who had received atovaquone-proguanil and the group who had received placebo did not differ significantly in rates of parasitemia (P=0.252). Adverse events during the chemosuppression phase did not differ between the groups.
Berman et al.[58] (2001) Atovaquone-proguanil 250 mg/100 mg daily for 8 days vs placebo	DB, PC, RCT Healthy, HIV-negative volunteers in the United States (US) aged 18-50 years Volunteers were challenged through the bites of mosquitoes infected with *P falciparum.*	N=16 8 weeks	Primary: Rates of parasitemia measured from blood films and by polymerase chain reaction (PCR), symptoms suggestive of malaria, adverse events not due to malaria	Primary: Patent parasitemia (i.e., confirmed by blood film) developed in 4 of 4 placebo recipients and 0 of 12 atovaquone-proguanil recipients (P<0.00l). Protective efficacy of atovaquone-proguanil was 100%. Evaluation of sub-patent parasitaemia by PCR analysis of blood obtained on Day 8 and Day 9 (6 and 7 days after challenge) was positive in 2 of 4 placebo recipients on Day 9 and negative on both days for all 12 atovaquone-proguanil recipients. Each placebo recipient was symptomatic within 6 hours of initial parasitaemia, with symptoms including fever, chills, vomiting, and other symptoms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mild gastrointestinal events were attributed to drug administration in 2 placebo recipients and 1 atovaquone-proguanil recipient.
Nakato et al.[64] (2006) Atovaquone–proguanil vs antimalarial chemoprophylaxis (chloroquine–proguanil or mefloquine) vs placebo	MA Patients at risk for malaria	N=4539 (10 trials) Variable duration	Primary: Prevention of malaria, adverse events and tolerability	Primary: <u>Atovaquone–proguanil vs placebo (5 studies)</u> The pooled relative risk of malaria in the intervention arm was 0.0423 (95% CI, 0.021–0.0853). The protective efficacy of atovaquone–proguanil was 95.8% (95% CI, 91.5–97.9). <u>Atovaquone–proguanil vs alternative antimalarial prophylactic agents (3 studies)</u> In only one of these three studies were any subjects diagnosed with malaria. In this one study, three subjects in the chloroquine–proguanil group developed *Plasmodium falciparum* malaria compared with none in the atovaquone–proguanil group. Although all three malaria cases were in the chloroquine–proguanil group, this was not statistically significant (P=0.25). There was no greater reporting of adverse effects in those taking atovaquone–proguanil compared with those taking placebo. Serious adverse events were rare. Only one adverse event related to atovaquone–proguanil was reported, and this was repeated vomiting requiring hospitalization. Patients on atovaquone–proguanil had fewer self-reported adverse effects (RR 0.8234; 95% CI, 0.67–1.01) and severe adverse effects (RR 0.61; 95% CI, 0.42–0.89) than those using other antimalarials, whereas neuropsychiatric adverse effects were similar (RR 0.74; 95% CI, 0.47-1.14). There was no significant difference in the proportion of study participants who completed their prescribed course (RR 0.88; 95% CI, 0.69–1.1).
Lobel et al.[30] (1993) Chloroquine 300 mg weekly	OS US Peace Corps volunteers in sub-Saharan Africa while taking	N=1,322 3 years	Primary: Long term efficacy and tolerability (incidence of *P falciparum* infections and of	Primary: Weekly mefloquine was 94% more effective compared to chloroquine (95% CI: 86 to 97, P<0.0001), 86% more effective compared to chloroquine plus proguanil (95% CI: 67 to 94, P<0.0001), and 82% more effective compared to mefloquine every other week (95% CI: 68 to 90; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs mefloquine 250 mg weekly vs mefloquine 250 mg every other week vs chloroquine 300 mg weekly and proguanil 200 mg daily	prophylactic therapy		adverse reactions)	No serious adverse events were observed and mild adverse events were equally frequent in mefloquine- and chloroquine-treated patients. The frequency of these events declined with the increasing duration of prophylaxis.
Tukur et al.[34] (2007) Chloroquine 600 mg base on days 1 and 2, followed by 300 mg base on day 3, then weekly pyrimethamine 25 mg until delivery (CQ+P) vs pyrimethamine-sulfadoxine 1,500 mg/75 mg as a single dose, then a second dose was administered in the	PRO Pregnant women between 12 and 28 weeks of gestation	N=500 Variable follow-up	Primary: Acute uncomplicated or severe malaria during pregnancy, infants born with congenital malaria parasitemia, and infants with low birth weight	Primary: Of the women who completed at least four antenatal visits, 26 (5.9%) had a febrile illness during follow-up: 4 (1.8%) in the SP group and 22 (9.8%) in the CQ + P group (P=0.005). None of the women in the SP group developed severe malaria, but 3 (1.3%) in the CQ + P group had severe malaria (P=0.25). Of those who completed at least four antenatal visits, no woman in the SP group but 11 women (4.9%) in the CQ + P group had peripheral parasitemia prior to or during delivery (P=0.002). Uncomplicated malaria was no more likely to occur in women in their first or second pregnancies than in women with two or more prior pregnancies (P=0.60). Of those who completed at least four visits, five (2.3%) in the SP group had minor reactions to the drug, most commonly vomiting and dizziness. Eleven (4.9%) in the CQ + P group had minor reactions, most commonly pruritus and vomiting. No woman discontinued prophylaxis because of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
third trimester a minimum of 4 weeks after the first dose but not after 34 weeks gestation as chemoprophylaxis (SP)				side effects. By delivery, the proportion of women with anemia decreased in both treatment groups. Significantly fewer women in the SP group had anemia (1.2%) than in the CQ + P group (5.0%; P=0.04). The mean hematocrit at delivery was 34.4% in the SP group compared with 33.7% in the CQ + P group (P=0.02). Two women in the CQ + P group delivered very low birth weight infants (<1,500 gm) at a gestational age of 30 weeks. Twelve subjects delivered low birth weight infants (<2,500 gm) between 30 and 35 weeks of gestation, six (3.5%) in the SP group and six (3.3%) in the CQ + P group (P=0.63). Low birth weight was not associated with maternal or cord blood parasitemia. The mean ± SD birth weight in the SP group was 3.12 ± 0.51 kg compared with 3.17 ± 0.56 kg in the CQ + P group (P=0.38).
Steffen et al.[26] (1993) Mefloquine vs pyrimethamine-sulfadoxine vs chloroquine-proguanil vs chloroquine vs no therapy	OS Tourists to East Africa; all passengers returning on charter flights from Mombasa, Kenya to Europe received an in-flight questionnaire and a second one was sent three months later. Respondents were excluded if they had spent more than a year abroad or if the majority of their stay was outside of East Africa.	N=145,003 1985-1991	Primary: Efficacy and side-effects of malaria prophylaxis	Primary: Among the 139,164 who stayed in East Africa for less than one year, 296 cases of confirmed malaria were reported (275 due to *P falciparum*). In people who used no chemoprophylaxis, the incidence of *P falciparum* malaria was 1.2% per month. Prophylactic effectiveness was 91% (95% CI: 85 to 94) for mefloquine, 82% (95% CI: 71 to 89) for pyrimethamine and sulfadoxine, 72% (95% CI: 56 to 82) for chloroquine plus proguanil, and 10% to 42% for chloroquine at various doses. Rates of side effects, which were usually mild, were 18.8% for mefloquine users, 17.1% and 18.6% for chloroquine 300 mg and 600 mg base per week users, 30.1% for chloroquine plus proguanil users, and 11.7% for sulfadoxine and pyrimethamine users.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ohrt et al.[27] (1997) Mefloquine 250 mg daily for 3 days, then 250 mg once weekly vs doxycycline 100 mg daily vs placebo	DB, PC, RCT Soldiers from military posts in areas of Indonesia where drug-resistant malaria is prevalent	N=204 13 weeks	Primary: First occurrence of malaria as documented by positive lab test Secondary: Tolerability of study drugs	Primary: In the placebo group, 53 of 69 soldiers developed malaria (9.1 person-years), resulting in an attack rate of 5.8 cases per person-year (95% CI: 4.3 to 7.7). No malaria occurred in the 68 soldiers (16.9 person-years) in the mefloquine group resulting in 100% (95% CI: 96 to 100) protective efficacy. In the doxycycline group, *P falciparum* malaria occurred in 1 of 67 soldiers (16.0 person-years), yielding a protective efficacy of 99% (95% CI: 94 to 100). Secondary: Both doxycycline and mefloquine were significantly better tolerated than placebo (P<0.001 and P=0.005, respectively) and doxycycline was better tolerated than mefloquine (P=0.006).
Sonmez et al.[29] (2005) Mefloquine 250 mg per week vs doxycycline 100 mg daily	RCT Prophylaxis in Turkish soldiers assigned to service in Kabul, Afghanistan	N=1,400 9 months (12 weeks prophylaxis and 6 months of monitoring after returning to Turkey)	Primary: Safety and efficacy of mefloquine and doxycycline	Primary: No malaria case was observed and there were no severe adverse events in either group. The most frequent side effects in both groups were gastrointestinal, for which the frequency was significantly higher with doxycycline (P<0.001). Neurological side effects were higher with doxycycline by the 2nd week compared to mefloquine (P=0.001). The compliance rate with mefloquine was greater than with doxycycline (P<0.05).
Soto et al.[28] (1998) Primaquine 30 mg daily vs	DB, PC, RCT Male Colombian soldiers assigned to patrol a malaria-endemic area (Uraba province, Columbia) receiving	N=176 19 weeks	Primary: Efficacy of primaquine prophylaxis	Primary: Protective efficacy in the primaquine group (122 participants) was 89% (95% CI: 75 to 96) against all types of malaria, 94% (95% CI: 78 to 99) against *P falciparum* malaria, and 85% (95% CI: 57 to 95) against *P vivax* malaria.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	required prophylactic therapy as nonimmune persons			
Treatment of Malaria				
Smithuis et al.[71] (2010) Artemether 3.3 mg/kg/day plus lumefantrine 19.8 mg/day (treatment 4) vs artesunate 4 mg/kg/day for 3 days plus mefloquine 25 mg/kg on day 0 (treatment 1a loose dose) vs artesunate 4 mg/kg/day for 3 days plus mefloquine 8.8 mg/kg/day for 3 days (treatment 1b fixed dose) vs artesunate 4	RCT, OL, MC Patients with acute uncomplicated *Plasmodium falciparum* malaria or mixed infection	N=800 63 days	Primary: Efficacy and safety	Primary: Patients on artesunate-amiodiaquine had a higher reoccurrence of *P falciparum* infections (9.4%; 95% CI, 5.7-15.3) than for artemether-lumefantrine (1.4%; 95% CI, 0.3-5.3%; P=0.0013), fixed-dose artesunate-mefloquine (0%; 95% CI, 0-2.3%; P<0.001), loose dose artesunate-mefloquine (1.3%; 95% CI, 0.3-5.3%; P=0.0018), and dihydroartemisinin-piperaquine (1.3%; 95% CI, 0.3-5.2%; P=0.0012). Artesunate-amiodiaquine compared with artesunate-mefloquine treatment groups (HR=3.2; 95% CI, 1.3-8.0; P=0.04). Artesunate-amiodiaquine compared with artemether-lumefantrine (HR=2.6; 95% CI, 1.0-6.0; P=0.08). Artesunate-amiodiaquine compared with dihydroartemisinin-piperaquine (HR=2.3; 95% CI, 0.9-6.0; P=0.08). Mixed *falciparum* and *vivax* infection were common: 16% had mixed infection at study initiation and 41% of patients had *Plasmodium vivax* infection at follow-up. The addition of single dose primaquine reduced *P falciparum* significantly (RR=11.9; 95% CI, 7.4-20.5). Adverse events reported by 599 patients; most common included vomiting and dizziness.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/day plus amiodiaquine 10.8 mg/kg/day (treatment 2) vs dihydroartemisinin 2.5 mg/kg/day plus piperaquine 20 mg/kg/day (treatment 3) Patients were also randomly assigned to receive primaquine 0.75 mg/kg as a single dose.				
Achan et al.[61] (2009) Artemether-lumefantrine (weight-based dosing) at baseline, then 8 hours after the first dose, then twice daily for the following two days vs quinine 10 mg/kg three times daily for 7 days	RCT, OL Children aged 6 to 59 months with uncomplicated malaria	N=175 28 days	Primary: Cure rates Secondary: Adherence to study drug, presence of gametocytes, recovery of hemoglobin concentration from baseline at day 28, and safety profiles	Primary: Cure rates were 96% for the artemether-lumefantrine group and 64% for the quinine group (P<0.001). Participants were 10 times more likely to fail treatment with oral quinine than with artemether-lumefantrine (HR 10.7; 95% CI, 3.3 to 35.5, P=0.001). The risk of treatment failure was significantly higher in the quinine group than in the artemether-lumefantrine group (35.3% vs 4.1%; P<0.001). Secondary: Mean adherence in the artemether-lumefantrine group was 95% and in the quinine group was 85% (P=0.0008). Non-adherence to treatment was higher in the quinine group than in the artemether-lumefantrine group (55% vs 17%; P=0.001). Gametocytemia was more common in the quinine group at day 7 compared with the artemether- lumefantrine group (14% vs 1%; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				By day 28 the groups did not differ. Total person time with gametocytes was 20 weeks for quinine compared with five weeks for artemether-lumefantrine (P<0.01). Hemoglobin concentrations improved equally in both groups during 28 days of follow-up. Reported adverse events did not differ between the groups. Common side effects of quinine such as nausea, headache, tinnitus, and blurred vision were not noted.
Gürkov et al.[63] (2008) Artemether-lumefantrine (AL) (weight-based dosing) at 0, 8, 24, 36, 48 and 60 hours (6 doses) vs atovaquone-proguanil (AP) 20 mg/8mg/kg (<40 kg) or 1000 mg/400 mg (adults and children ≥40 kg) per day for 3 days vs quinine (Q) 10 mg/kg (children) or 600 mg (adults and	RCT, SB Patients ≥5 years of age with parasitologically proven uncomplicated *P. falciparum* malaria	N=97 90 days	Primary: Clinical and parasitological efficacy, tolerability, and ototoxicity	Primary: On day 7, no treatment failure was detected in any group. Until day 28, three patients in the Q group and one in the AP group presented with *P. falciparum* malaria. The parasitological failure rate on day 28 was 9% and 6% in the Q and AP group, respectively. There was no treatment failure in the AL group. Between day 28 and day 90, seven patients with *falciparum* malaria were diagnosed. Nine patients (five treated with Q, two with AP, and two with AL) showed *P. vivax* infection during follow-up. No vomiting occurred after ingestion of the antimalarial drugs, and no serious adverse events were reported during treatment and follow-up. Hearing problems and tinnitus were more common on day 7 with nine of thirty patients complaining of hearing problems in the Q group. In seven of these, audiometry and otoacoustic emissions (OAE) testing confirmed significant hearing loss. Patients reporting subjective hearing impairment in the AL group did not have abnormal hearing test results. In the AP group, only the reported hearing loss by one patient on day 90 corresponded to significantly impaired audiometry and OAE results. In the Q group, a hearing loss affecting all frequencies was evident on day 7 and has disappeared by day 28. Otherwise, no significant changes of the mean hearing thresholds compared to day 0 were evident. There was no evidence of persistent hearing loss in any treatment group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
children ≥50 kg) three times daily for 7 days				The average distortion product (DP) threshold level of the Q group on day 7 was elevated from baseline. Multivariate analysis reveals a significant effect of time on the DP threshold levels for day 7 and day 28. The three treatment groups did not behave differently, except on day 7 when a significant combined effect of time and group is visible as the Q ototoxicity. There was no evidence of drug-induced brain stem lesions by brain stem evoked response audiometry (BERA) measurements.
Thapa et al.[62] (2007) Artemether-lumefantrine (AL) (based on body weight) given as 6 doses over 3 days vs pyrimethamine-sulfadoxine (SP) (based on body weight) as a single dose	RCT, OL, PG Patients >5 years of age who had uncomplicated *falciparum* or mixed *falciparum/vivax* malaria infection	N=99 28 days	Primary: Treatment failure	Primary: Assessed by microscopy, 12.1% of SP-treated patients redeveloped parasitemia during the 28-day follow-up period compared with 0% in the AL group (P=0.011). An additional six patients (two SP and four AL) with sub-microscopic gametocytemia or breakthrough parasitemia between Days 14 and 28, suggesting that AL efficacy was lower than estimated by microscopy. Apart from fever, the most frequent symptoms at presentation were headache (97% and 88% in AL and SP groups, respectively), nausea (42% and 64%, respectively), and vomiting (39% and 46%, respectively). Other gastrointestinal, neurologic, musculoskeletal, respiratory, and dermatologic complaints were less frequent.
Bustos et al.[39] (1999) Atovaquone-proguanil (weight-based dosing) daily for 3 days vs chloroquine (total dose over the	OL, RCT Patients with acute uncomplicated *P falciparum* malaria treated at a hospital in the Philippines between October 1994 and February 1995, 12-65 years old and >30 kg	N=110 28 days	Primary: Cure rate including parasite clearance time (PCT) and fever clearance time (FCT); symptoms were also assessed using an interview	Primary: Atovaquone-proguanil produced a significantly higher cure rate (100%) compared to chloroquine (30.4%; P<0.001) or the chloroquine-sulfadoxine-pyrimethamine regimen (87.5%; P<0.05). There were significant differences between the treatment groups regarding parasite clearance time (mean: 46.7 hours for atovaquone-proguanil, 60 hours for chloroquine, and 42.8 hours for chloroquine plus sulfadoxine-pyrimethamine) or fever clearance time (mean, 38.8, 46.8, and 34.5 hours, respectively). The most frequently reported adverse events were consistent with malaria

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
course of 3 days: if >40 kg, received 1,500 mg, if 30-40 kg received 10 mg/kg) vs chloroquine (dosed as above) plus pyrimethamine-sulfadoxine (>50 kg 1,500 mg/75 mg; ≤50 kg 1,000 mg/50 mg) as a single dose	Patients were hospitalized for 28 days to ensure medication compliance and prevent reinfection.			infection and included vomiting (18% with atovaquone-proguanil, 17% with chloroquine, and 9% with chloroquine-sulfadoxine-pyrimethamine), abdominal pain (15%, 17%, and 3%, respectively), anorexia (11%, 13%, and 0%, respectively), and headache (6%, 17%, and 3%, respectively). Adverse events did not differ significantly between treatment groups.
Looareesuwan et al.[40] (1999) Atovaquone-proguanil 4 tablets by mouth daily for 3 days vs mefloquine 750 mg by mouth initially, then 500 mg 6 hours later	OL, RCT Adult patients with acute *P falciparum* malaria treated at a hospital in Thailand between August 1993 and July 1994 Patients were treated for 1-3 days and followed for 28 days.	N=158 28 days	Primary: Cure rate, calculated using World Health Organization (WHO) classifications as R1, R2 or R3 Secondary: Parasite clearance time (PCT), fever clearance time (FCT), safety	Primary: Atovaquone-proguanil was significantly more efficacious compared to mefloquine (cure rate 100% vs 86%; P<0.002). Secondary: The treatments did not differ with respect to PCT (mean 65 hours compared to 74 hours) or FCT (mean 59 hours compared to 51 hours). Adverse events occurred in 36% of the patients in the atovaquone-proguanil group and 35% of those in the mefloquine group, with the chief difference observed being vomiting which was found to be more common in the atovaquone-proguanil group (10% vs 2%).
Hitani et al.[41] (2006) Atovaquone-proguanil 250 mg/100 mg 4	RCT Nonimmune patients with uncomplicated *P falciparum*	N=73 Follow-up period was 7-10 days	Primary: Cure rate, parasite clearance time (PCT), fever clearance time (FCT), and adverse	Primary: All 20 atovaquone-proguanil adult patients (100%) and 49 of the 50 mefloquine-treated patients (98%) were cured (P=0.71). In the atovaquone-proguanil group, the FCT and PCT appeared to be longer than those of the mefloquine group (3.7 and 3.3 days compared to

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tablets daily for 3 successive days (children received one tablet daily for 3 successive days) vs mefloquine 15-25 mg/kg divided into 1-3 doses			events	2.9 and 2.8 days, P=0.13 and 0.28). Transient elevations in liver enzymes were noted in 15% of the atovaquone-proguanil-treated patients while 38% of mefloquine-treated patients experienced other adverse events such as dizziness, nausea, and vomiting.
de Alencar et al.[42] (1997) Atovaquone 1g plus proguanil 400 mg, both once daily for 3 days vs quinine 600 mg 3 times daily plus tetracycline 250 mg 4 times daily, both for 7 days	OL, R Adult men (ages 18–65 years) with smear-confirmed *P falciparum* malaria undergoing treatment for malaria at a hospital in the southern Brazilian Amazon region	N=175 10 months (study duration) 28 days (per-patient treatment and follow-up)	Primary: Fever clearance times, parasite clearance times, cure rates, adverse events	Primary: All patients in the quinine plus tetracycline group were cured, and 1 patient had recrudescence in the atovaquone plus proguanil group. This gave a cure rate of 100% (95% CI: 95 to 100) for the quinine plus tetracycline group and 98.7% (95% CI: 92 to 99) for the atovaquone plus proguanil group. The mean parasite clearance times were shorter in the atovaquone plus proguanil group (56.1 hours) than in the quinine plus tetracycline group (64 hours; P=0.008). The mean fever clearance times were shorter in the atovaquone plus proguanil group (18.8 hours) than in the quinine plus tetracycline group (28.5 hours, (P=0.05). Approximately 62% of patients had side effects in the atovaquone plus proguanil group vs 89% in the quinine plus tetracycline group. There were more patients complaining about tinnitus (55 vs 3; P=0.01), dizziness (39 vs 10; P=0.01), nausea (22 vs 12; P=0.05), and anorexia (13 vs 5; P=0.04) in the quinine plus tetracycline group than in the atovaquone plus proguanil group.
Llanos-Cuentas et al.[47] (2001) <u>Phase I</u>	OL, RCT Patients with acute *falciparum* malaria in northern Peru	N=43 Duration not reported	Primary: 28-day cure rate (RIII=no significant reduction in	Primary: <u>Phase I</u> Significantly more patients in the atovaquone-proguanil group were cured (100% vs 8%, P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atovaquone-proguanil vs chloroquine <u>Phase II</u> pyrimethamine-sulfadoxine as a single dose vs atovaquone-proguanil			parasitemia in first 48 hours, RII= marked reduction of parasitemia without clearance in 7 days, RI= clearance of parasitaemia within 7 days followed by recrudescence in 28 days) Secondary: Fever clearance time and parasite clearance time	<u>Phase II</u> There were no significant differences in cure rates between the treatment groups (100% vs 100%). Secondary: There were no significant differences in parasite clearance times or fever clearance times between groups in either phase of the study.
Krudsood et al.[59] (2007) Atovaquone-proguanil 1,000 mg/400 mg once a day for three days	OL Individuals greater than 14 years of age with confirmed acute, uncomplicated *P falciparum*	N=140 3 treatment days followed by 3 weeks in a non-transmission area	Primary: 28 day cure rate, parasite clearance time (PCT), and fever clearance time (FCT)	Primary: The overall cure rate at the 28-day follow-up was 97.8% (95% CI: 95.4 to 100). Mean PCT was 41.9 hours while the FCT was 37.1 hours.
Mulenga et al.[60] (1999) Atovaquone-proguanil vs pyrimethamine-sulfadoxine	OL, PG, RCT Inpatients at the Central Hospital of the Tropical Disease Research Centre in Ndola, Zambia with acute *P falciparum* malaria (parasite counts between 1,000 and 200,000/ul of blood)	N=163 28 days after treatment ended	Primary: 28 day cure rate, parasite clearance time (PCT) and fever clearance time (FCT)	Primary: There was no significant difference in cure rates between the atovaquone-proguanil group and the sulfadoxine-pyrimethamine group after 28 days (100% vs 98.8%, respectively). FCT was significantly shorter in the atovaquone-proguanil group compared to the sulfadoxine-pyrimethamine group (mean, 30.4 vs 44.9 hours; 95% CI: 8.3 to 26.5; P<0.05). PCT was significantly longer in the atovaquone-proguanil group compared to the sulfadoxine-pyrimethamine group (mean, 64.0 vs 51.4 hours; 95% CI: 12 to 24; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mulenga et al.[65] (2006) Atovaquone–proguanil (AP) 17 mg/kg and 7 mg/kg of atovaquone and proguanil, respectively once daily for 3 days plus placebo vs pyrimethamine-sulfadoxine (SP) 25 mg/kg of sulfadoxine as single dose plus placebo Folic acid 1 mg was given daily for 14 days.	RCT, DB Children 6-119 months of age with moderately severe anemia (packed cell volume of <21% and >9%) and *P. falciparum* parasitaemia	N=128	Primary: Treatment failure (defined as a need for blood transfusion or treatment with quinine, persistent anemia or death within 14 days) Secondary: Fever clearance time, parasitemia at days 3, 7, 14 and 28 after the start of treatment, hematological findings 14 or 28 days after the start of treatment, and adverse events	Primary: By day 14, 22% of children who had received SP as compared with 8% of children who had received AP met the criteria for treatment failure (OR 3.34; 95% CI, 1.54-7.21). Secondary: The fever clearance time (FCT) was faster in the AP group than in the SP group (P=0.0001). The median FCT in the AP group was 12 hours compared with 29 hours in the SP group. At each time point, parasitaemia was less frequent in children who received AP than in those who received SP, but the difference was only statistically significant at day 28 when the failure rate in the SP group was 22% (P=0.001). There were no significant differences in hematological measurements between the treatment groups. The occurrence of non-serious adverse events (AEs) such as cough, vomiting, anorexia and weakness was comparable in the two treatment groups with the exception of vomiting. More patients in the AP group (19%) vomited between day 1 and 2 than those in the SP group (7%; P=0.003). AEs were mild and self-limiting and required no intervention.
Ursing et al.[10] (2011) Chloroquine 50 mg/kg given as 2 daily doses over 3 days vs artemether-lumefantrine 1-4	RCT, OL, MC Children aged 6 months to 15 years with uncomplicated *falciparum* malaria	N=378 1.5 years	Primary: PCR-adjusted adequate clinical and parasitological response (ACPR) on day 42; PCR-adjusted ACPR on days 28 and 70; selection of resistance-associated alleles and drug	Primary: Day 28 and 42 treatment efficacies were 97% and 97%, respectively, for artemether-lumefantrine; 95% and 94% respectively, for chloroquine. Parasite clearance was faster with artemether-lumefantrine than with chloroquine (P<0.001). Symptoms resolved similarly in both treatment arms during days 0–3. In the artemether-lumefantrine arm, dizziness (P=0.03) and headache (P=0.01) were more common on day 1. Sleeping disorders were more common in the chloroquine arm on day 2 (P=0.003). Fever was cleared by 130 of 181 and 143 of 188 children by the second dose in the chloroquine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tablets per dose according to weight were given at 0, 8, 24, 36, 48, and 60 hours			tolerability	and artemether-lumefantrine arms, respectively (P=0.78). When parasites with resistance-associated *pfcrt* 76T were treated, the day 28 efficacy of chloroquine was 87%. No severe drug-related adverse events were detected for either treatment.
Lederman et al.[35] (2006) Chloroquine 25 mg/kg for 3 days vs chloroquine (same dose) and sulfadoxine 25 mg/kg (single dose) and pyrimethamine 1.25 mg/kg (single dose) (SP) vs above therapy and primaquine 45 mg on day 0 vs above therapy and primaquine 45 mg on day 2	MC, RCT Patients with uncomplicated *falciparum* malaria in Indonesia	N=117 28 days	Primary: Clearance rates and reinfection adjusted cure rates	Primary: After 28 days, 58% of subjects receiving chloroquine had cleared parasitemia and remained aparasitemic compared to 94% receiving chloroquine plus SP (P<0.001). Genotyping was used to confirm that no new infections had intervened to influence cure rates. The demonstrated reinfection-adjusted cure rates for chloroquine compared to chloroquine plus SP were 70% and 99%, respectively (P=0.0006). The difference in clearance rates between the two primaquine groups was insignificant (P=0.025).
Yeshiwondim et al.[11] (2010)	RCT, OL, PRO Ethiopian patients	N=290 8 months	Primary: Treatment failure and relapse rates	Primary: A total of 98.6% patients cleared parasitemia on day 3. There was no difference in mean parasite clearance time between treatment groups

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Chloroquine 10 mg/kg on day 0 and day 1 and 5 mg/kg on day 2 plus primaquine 0.25 mg/kg from day 29 to day 41 vs chloroquine 10 mg/kg on day 0 and day 1, and 5 mg/kg on day 2 plus primaquine 0.25 mg/kg from day 3 to day 16	≥1 year of age who were positive for *P. vivax* infections			(chloroquine: 48.3 hours and chloroquine+ primaquine 50.67 hours; P=0.25). The cumulative incidence for therapeutic failure at day 28 was 5.76%, (95% CI, 2.2–14.61) with chloroquine treatment and 0.75% (95% CI, 0.11–5.2) with chloroquine + primaquine treatment (P=0.19). The relapse rate was 8% for chloroquine treatment and 3% for chloroquine + primaquine treatment (P=0.07). The cumulative risk of relapse at day 157 was 61.8% (95% CI, 20.1–98.4) with chloroquine treatment compared with 26.3% (95% CI, 7.5–29.4) with chloroquine + primaquine treatment (P=0.0038).
Adam et al.[36] (2004) Chloroquine 10 mg/kg for 2 days then 5 mg/kg on day 3 vs pyrimethamine-sulfadoxine as a single dose of 25 mg/kg of the sulfadoxine component (SP) vs	OL, RCT Patients with uncomplicated *P falciparum* malaria in Sudan	N=96 28 days	Primary: Clinical response according to WHO criteria and parasitological response (levels RIII, RII, and RI), gauged by readings taken on days 0–7, 14, 21 and 28 (RIII if day-2 parasitemia was >25% of day 0; RII if positive smear on day 2 and parasitemia <25% of day 0 value or smear-positive on days 2–7; RI if	Primary: No treatment failures were observed among the patients given sulfadoxine and pyrimethamine. In the chloroquine group, 23.1% had an adequate clinical response; however, 15.4% had early failure (severe malaria symptoms on day 3, day-2 parasitaemia was >25% of day 0, or day-3 parasitaemia was >25% of day 0) and 61.5% late treatment failure (fever or severe malaria symptoms or any parasitemia after day 3). Regarding, parasitological failure, 54.1% in the chloroquine group showed early resistance, 7.7% showed late RI, and 15.1% showed RIII. Adequate treatment responses were achieved in 90.6% of the quinine group. The frequency of treatment failure was significantly higher with chloroquine compared to quinine (76.9% vs 9.3%; P=0.0008).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
quinine 10 mg/kg three times a day for 1 week			clearance of parasitemia for at least two consecutive days followed by the reappearance of parasitemia either on days 7 or 14 [early RI] or on days 21 or 28 [late RI])	
Leslie et al.[68] (2009) Chloroquine (250 mg base) in divided doses over 3 days vs chlorproguanil-dapsone (2.0 and 2.5 mg/kg per day, respectively) at 24-hour intervals over 3 days vs sulfadoxine-pyrimethamine (25 and 1.25 mg/kg, respectively) as a single dose on day	RCT, OL Patients ≥3 years of age with microscopically confirmed *P vivax* malaria	N=767 28 days	Primary: Complete clearance of parasites by day 14 Secondary: Parasite-free by day 28, clinical failure, and anemia	Primary: All patients completely cleared parasites by day 14 and all 3 study drugs were equally and highly effective. Secondary: By day 28, treatment failure was found in 9.9% of chlorproguanil-dapsone treated patients, which was less effective than sulfadoxine-pyrimethamine (OR 6.4; 95% CI, 2.4-17.0; P<.001) and chloroquine (OR, 8.4; 95% CI, 2.0-36.5; P=.004). Chloroquine failure rates (1.3%) and sulfadoxine-pyrimethamine failure rates (1.7%) were similar (OR, 1.3; 95% CI, 0.3-7.0; P=0.73). Clinical failure rates were comparable between treatment groups up to days 14 and 28. Anemia varied by study drug over time, with chloroquine associated with the lowest rates of anemia. Chloroquine was associated with the lowest frequency of any adverse events. The frequency of nausea and vomiting was higher in the chlorproguanil-dapsone group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0, followed by placebo for 2 days				
Ezedinachi et al.[37] (1999) Mefloquine 250 mg, sulfadoxine 500 mg and 25 mg pyrimethamine as a single-dose tablet; 0.5-2 tablets were taken daily based on body weight (MSP) vs chloroquine 10mg/kg for 2 days then 5 mg/kg on day 3 (CQ)	MC, RCT Patients with malaria in Nigeria, each treatment was divided into two groups (Group 1 was treated presumptively, based on symptoms while Group 2 was treated based on a parasitological diagnosis)	N=1,935 12 months	Primary: Efficacy and tolerability of treatments	Primary: Low-dose MSP had day-7 response rates of 95% and 91% for Group 1 and Group 2. CQ had day-7 response rates of 82% and 66% in Group 1 and Group 2, respectively. The low-dose MSP was significantly more efficacious, with faster fever and parasite clearance times compared to CQ (P<0.0001). Adverse events were generally more common among those treated with MSP (29%) than those treated with CQ (17%, P<0.0001); however, the adverse events caused by both drugs were mild to moderate and self-limited.
Maguire et al.[38] (2006) Mefloquine 15 mg/kg as a single dose vs chloroquine 150 mg base in 3 doses over 48 hours: 10 mg/kg on day 0, then 10 mg/kg on day 1, then 5 mg/kg on day 2	OL, PRO, RCT A malaria-naïve population of Javanese adults and children were monitored after arriving in a malaria-endemic region of Papua, Indonesia; all subjects who contracted uncomplicated malaria within this group were included in the study	N=243 3 years	Primary: Curative efficacy at 28 days	Primary: The cumulative 28-day curative efficacy with mefloquine was 96% against *P falciparum* malaria and 99.6% against *P vivax* malaria compared to 26% and 82% with chloroquine against *P falciparum* malaria and *P vivax* malaria, respectively (P<0.05). The relative rates of treatment failure with chloroquine compared to mefloquine were 20 for *P falciparum* (95% CI: 10 to 41) and 52 for *P vivax* (95% CI: 7 to 376).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Subjects with confirmed *P vivax* malaria also received primaquine.				
de Radigues et al.[43] (2006) Pyrimethamine-sulfadoxine as a single dose of 25 mg/kg of the sulfadoxine component (SP) vs chloroquine 10 mg/kg day 0 and day 1, and 5 mg/kg day 2 (CQ)	RCT Children 6-59 months with *P falciparum* malaria	N=210 28 days	Primary: Therapy failure	Primary: Not taking into account reinfections the global failure rate at day 14 was 2.0 (95% CI: 0.0 to 4.8) in the SP group and 44.2% (95% CI: 34.9 to 96.2) in the CQ group. At day 28 adjusted failure proportions were 7.0% (95% CI: 1.9 to 12.1) in the SP group and 90.5% (95% CI: 84.8 to 96.2) in the CQ group.
MacArthur et al.[44] (2001) Pyrimethamine-sulfadoxine as a single dose of 25 mg/kg of the sulfadoxine component (SP) vs mefloquine 15 mg/kg (MQ)	RCT Children 6-59 months with *P falciparum* malaria	N=102 14 days	Primary: Clinical response, parasitological response, hematologic response, and adverse events	Primary: There was no significant difference in clinical, parasitological, and hematologic response between the two treatment groups (P=0.43, 0.69, and 0.70). Significantly more children vomited while on SP compared to MQ on day 2 (P=0.047) and between days 3 and 7 (P=0.039).
Marquiño et al.[45]	MC, RCT	N=198	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2003) Pyrimethamine-sulfadoxine as a single dose of 25 mg/kg of the sulfadoxine component (SP) vs chloroquine 10 mg/kg day 0 and day 1, and 5 mg/kg day 2 (CQ) vs mefloquine single dose of 15 mg/kg (MQ)	Patients 2-50 years of age with *P falciparum* malaria	14 days	Treatment failures	An early treatment failure was noted in 27.1% of the CQ group compared to 0% in the SP or MQ. A late treatment failure was noted in 59.3% of the CQ group, 6.4% in the SP groups and 0% in the MQ group.
Leslie et al.[46] (2007) Pyrimethamine-sulfadoxine as a single dose of 25 mg/kg of the sulfadoxine component (SP) vs chloroquine 250 mg in divided doses over 3 days (CQ)	OL, RCT Individuals older than 3 years of age with *P vivax* malaria	N=767 28 days	Primary: Parasitological failure by day 14 Secondary: Parasitological and clinical failure by day 28	Primary: Only 1 patient in the SP group had a failure by day 14. Secondary: Failure rates by day 14 were 1.3% in the CQ group, 1.7% in the SP group, and 9.9% in the CD group. CD was less effective than SP (OR: 6.4, 95% CI: 2.4 to 17; P<0.001), and CQ (OR: 8.4, 95% CI: 2.0 to 36.5; P=0.004). There was no significant difference between CQ and SP at day 28 (OR: 1.3, 95% CI: 0.3 to 7.0; P=0.73).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs chlorproguanil-dapsone 2.0 and 2.5 mg/kg/day for 3 days (CD)				
Bell et al.[69] (2008) Pyrimethamine-sulfadoxine as a single dose of 25 mg/kg of the sulfadoxine component (SP) vs chloroquine 10 mg/kg (CQ) on days 0 and 1, and 5 mg/kg on day 2 plus SP vs artesunate 4 mg/kg (ART) once daily for 3 days plus SP vs amodiaquine 10 mg/kg (AQ) daily for 3 days plus SP	RCT, DB Children aged 1-5 years with an illness suggesting *falciparum* malaria	N=455 42 days	Primary: Day 28 ‘‘adequate clinical and parasitological response’’ (ACPR) rate Secondary: Day 14 and 42 ACPR rates, time to fever resolution, time to parasite clearance, change in hemoglobin from day 0 to day 14, appearance of gametocytes by day 28 after treatment, and adverse events	Primary: The day 28 ACPR rate was 25% with SP alone, which was less effective than each of the three SP combination regimens (P<0.001). AQ+SP had an ACPR rate of 97%, which was higher than CQ+SP and ART+SP (P<0.001). There was no significant difference in the day 28 ACPR rate between CQ+SP and ART+SP. Secondary: Ninety-five percent of children had cleared their parasite by day 2 in the ART+SP group compared to 35% for SP, 47% for CQ+SP, and 55% for AQ+SP (P<0.001 for each comparison with AQ+SP). By days 3 and 7, there were no differences between the three combination therapies and they were all more effective than SP alone (P=0.005). In the SP group, there was no association between the day 0 parasitaemia and time to parasite clearance or between day 0 parasitaemia and clinical outcome. Fever resolution was slower with SP alone; the percentage of children who still had fever on day 1 were 18% for SP, 5% for CQ+SP, 6% for ART+SP and 5% for AQ+SP (P<0.008 for each comparison with SP). Mean hemoglobin concentration rose in all treatment groups. Compared to SP alone, the adjusted mean on day 14 was greater after CQ+SP (P=0.03) and AQ+SP (P=0.002) but not after ART+SP (P=0.81). Gametocytes were present on day 0 in 16% of children. There were no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				differences between the groups in the percentage of children with gametocytes on day 28; 4% after SP, 7% after CQ+SP, 5% after ART+SP and 7% after AQ+SP. Cough was the most common adverse event (45% of all AEs). Compared to SP alone, cough was more commonly reported after ART+SP (P=0.04). No other statistically significant differences were found.
Achan et al.[72] (2009) Quinine 10 mg/kg/day 3 times daily for 7 days vs artemether-lumefantrine: 1 tablet per dose for body weight 10-14.9 kg, 2 tablets for 15-24.9 kg, 3 tablets for 25-34.9 kg, 4 tablets for ≥ 35kg for 7 days	RCT, OL Ugandan children 6 to 59 months with uncomplicated malaria	N=175 240 days	Primary: Parasitological cure rates after 28 days of follow-up Secondary: Adherence to study drug, presence of gametocytes, recovery of hemoglobin concentration from baseline at day 28 and incidence of adverse effects	Primary: Unadjusted cure rate by genotyping was 96% for the artemether-lumefantrine group compared with 64% in the quinine group (P=0.001). In the quinine group, 69% of parasitological failures were due to reoccurrence compared with none in the artemether-lumefantrine group. Secondary: The mean adherence to artemether-lumefantrine was 94.5% compared with 85.4% to quinine (P=0.0008). Adherence levels ≥80% was associated with a decreased risk of treatment failure (P=0.06). Adverse events did not differ between treatment groups.
Piola et al.[18] (2010) Quinine 10 mg/kg every 8 hours for 7 days vs artemether-lumefantrine	RCT, OL Pregnant Ugandan women with uncomplicated *Plasmodium falciparum* malaria	N=304 2.5 years	Primary: Adjusted cure rate at day 42	Primary: At day 42, 99.3% of patients taking artemether–lumefantrine and 97.6% taking quinine were cured (lower limit of 95% CI, 0.9). The median time to first *P falciparum* reappearance was 65 days for quinine and 70 for artemether–lumefantrine (P=0.4). On day 2, parasite clearance was lower in the quinine group than in the artemether–lumefantrine group (P<0.0001), but increased on day 3. Artemether–lumefantrine was more effective than quinine in gametocyte

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(fixed-dose combination of 20-120 mg) 4 tablets at 0, 8, 24, 36, 48, and 60 hours for 3 days				clearance by day 2 (P=0.03) and day 7 (P=0.04). A total of 290 adverse events in the quinine group and 141 in the artemether–lumefantrine group.
Malaria (Relapse Prevention)				
Galappaththy et al.[48] (2007) Trial Group 1: Primaquine 5mg/kg/day plus chloroquine 25 mg/kg/day vs chloroquine alone Trial Group 2: Primaquine 15 mg/kg daily plus chloroquine for 5 vs 14 days	MA Studies evaluating relapse prevention	N=3,423 (9 trial) 5-14 days	Primary: Relapse prevention	Primary: Compared with chloroquine alone, 5-day primaquine plus chloroquine was no better at preventing relapses (OR 1.04); however, the 14-day primaquine plus chloroquine treatment regimen was significantly better (OR 0.24, 95% CI: 0.12 to 0.45) at preventing relapse. Direct comparisons of the 14-day and 5-day primaquine plus chloroquine regimens also confirmed the greater efficacy of the longer course (OR 13.33, 95% CI: 3.45 to 51.44).
Treatment of Lupus Erythematosus				
Tsakonas et al.[49] (1998) Hydroxy-chloroquine 400 mg daily (HCQ) vs	PC, RCT Patients with quiescent systemic lupus erythematosus (SLE)	N=47 42 months	Primary: Time to major flare-up Secondary: Specific subtype flares (glomerulo-nephritis, vasculitis, etc) and hospitalization for	Primary: Over the 42 months of study, 50% in the placebo group and 28% of patients in the treatment group experienced a major flare. The relative risk of major flare for those randomized to continue HCQ vs placebo was 0.43 (95% CI: 0.17 to 1.12). Secondary: The relative risks for subtypes of flares were 0.26 (95% CI: 0.03 to 2.54) for nephritis, 0.51 (95% CI: 0.09 to 3.08) for vasculitis and 0.65 (95% CI:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			an SLE exacerbation	0.17 to 2.41) for flares characterized by other symptoms. The relative risk of hospitalization for major flare for patients randomized to continue hydroxychloroquine was 0.58 (95% CI: 0.13 to 2.60).
Molad et al.[50] (2002) Hydroxy-chloroquine (as a component of ongoing therapy for SLE) vs non-hydroxy-chloroquine-containing regimens	OBS Patients with systemic lupus erythematosus (SLE)	N=151 Variable duration	Primary: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI)	Primary: Mean score of SLICC/ACR DI at the first and last encounters were 0.17 and 1.64, respectively (P<0.0001). Hydroxychloroquine therapy was significantly associated with lower SLICC/ACR DI (P=0.015). Hydroxychloroquine treatment significantly prolonged damage-free survival in the lupus patients (P<0.0001).
Ruiz-Irastorza et al.[12] (2010) Hydroxy-chloroquine treatment vs chloroquine treatment	MA Patients with systemic lupus erythematosus (SLE)	95 trials Variable duration	Primary: Efficacy and safety	Primary: High levels of evidence were found that antimalarials prevent lupus flares and increase long-term survival of patients with SLE. Moderate evidence of protection from antimalarials against irreversible organ damage, thrombosis and bone mass loss. High levels of evidence were found that hydroxychloroquine decreases lupus activity without harming pregnant women or their baby. Evidence supporting an effect on severe lupus activity, lipid levels and subclinical atherosclerosis was weak.
Treatment of Rheumatoid Arthritis				
Suarez-Almazor et al.[51] (2000) Hydroxy-	MA Patients with recently diagnosed, mild rheumatoid	N=571 (4 trials) ≥6 months	Primary: End-of-trial results were pooled as standardized mean differences	Primary: The standardized mean differences (SMDs) for the various outcome measures were as follows: tender joints: –0.33 (95% CI: –0.50 to –0.17); swollen joints: –0.52 (95% CI: –0.69 to –0.36); pain: –0.45 (95% CI: –0.63 to –0.27); physician global assessment: –0.45 (95% CI: –0.66 to –

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chloroquine 400 mg daily vs placebo	arthritis with no prior treatment with a disease-modifying antirheumatic drug (DMARD)		(SMDs) for joint scores, pain, global, and functional assessments	0.24); patient global assessment: –0.39 (95% CI: –0.59 to –0.18). A weighted mean difference (WMD) of 6 mm (95% CI: –8.51 to –4.24) favoring hydroxychloroquine was observed for erythrocyte sedimentation rate (ESR). Only one study measured functional status: no significant differences were observed between hydroxychloroquine and placebo in Health Assessment Questionnaire (HAQ) scores. Another study reported radiological progression but no significant differences were observed between groups. Patients receiving hydroxychloroquine were less likely to discontinue treatment, overall (OR 0.59, 95% CI: 0.41 to 0.86), or because of insufficient response (OR 0.55, 95% CI: 0.33 to 0.91). Withdrawals due to adverse reactions were rare (4.7% in the antimalarial group and 5.5% in the placebo group). None of the 3 studies which conducted ophthalmologic evaluations reported withdrawals due to ocular toxicity.
Matteson et al.[52] (2004) Hydroxy-chloroquine 200 mg twice daily, NSAID, and prednisone up to 10 mg daily	OL Patients with early rheumatoid arthritis (less than 1 year); all patients had never taken any standard disease-modifying anti-rheumatic drug (DMARD) prior to enrollment	N=111 24 weeks	Primary: Baseline factors associated with initial response to treatment; if patients needed to add methotrexate (MTX) or prednisone >10 mg/day they were also classified as nonresponders	Primary: After 24 months of follow-up, a majority of patients (56/94) were either still on solo DMARD therapy with HCQ (N=49) or off DMARD therapy with controlled/quiescent disease (N=4), and 38 patients were taking MTX (including 11 in combination with other DMARDs). Features present at enrollment which were predictors of MTX therapy at month 24 weeks were high pain score, baseline rheumatoid factor titer >1:40, higher number of swollen joints, and poor patient global assessment (P<0.001).
Verstappen et al.[53] (2005) Hydroxy-	MC, RCT Patients with recent onset of rheumatoid	N=562 62 months	Primary: Remission rates (duration of morning stiffness	Primary: Thirty-six percent of patients achieved at least one period of remission. The percentage of patients in remission during follow-up was not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chloroquine 400 mg/day vs intramuscular gold 50 mg/week vs methotrexate 7.5–15 mg/week vs NSAIDS	arthritis (within 1 year)		<15 minutes, visual analog scale pain <10 mm, Thompson joint score=10, and ESR=30 mm/hour) for at least 6 months	significantly different between the four treatment groups: 42% in the gold group, 36% in the methotrexate group, 31% in the hydroxychloroquine group, and 38% in the pyramid group (P=0.28). Median duration between diagnosis and the first remission period was 15 months for the intramuscular gold group, 18 months for the methotrexate and hydroxychloroquine groups, and 24 months for the pyramid group (NS). Predictors of remission were early response to initial treatment, less pain, rheumatoid factor negativity, and lower joint score at baseline (P<0.0001).
Das et al.[66] (2007) Hydroxy-chloroquine 400 mg daily for 8 weeks (HCQ) vs placebo for 8 weeks After 8 weeks, all patients received hydroxy-chloroquine 200 mg daily for 4 weeks. All patients received nimesulide 100 mg	RCT, DB, MC, PC Patients between 18 and 60 years of age suffering from rheumatoid arthritis (RA) who had failed to respond to at least 2 weeks of NSAID therapy	N=122 12 weeks	Primary: Assessment of response at 12 weeks using modified ACR 20 (American College of Rheumatology 20) criteria	Primary: A significant improvement was recorded in the HCQ group as compared to placebo in swollen joint count (57.9% vs 37.9%; P=0.03), tender joint count (52.6% vs 29.3%; P=0.01) and VAS pain score (57.9% vs 31.0%; P=0.004). There were no significant differences between the treatment groups in physician global assessment (49.1% vs 32.8%; P=0.07), ARA functional class (45.6% vs 29.3%; P=0.07), patient global assessment (50.9% vs 37.9%; P=0.16), or ESR (42.1% vs 34.5%; P=0.4). Overall improvement (Modified ACR 20 Response) was observed in 40.4% of patients in the HCQ group as compared to only 20.7% of patients in the placebo group (P=0.02). At 12 weeks of study, no clinically significant biochemical changes from baseline were observed in patients treated with HCQ. The ophthalmic examination carried out also did not show any abnormal findings in any of the patients. Only minimal adverse events were seen in the study and the most common

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
twice daily.				were gastrointestinal.
Saunders et al.[67] (2008) Methotrexate (MTX) 7.5 mg/week, sulfasalazine (SSZ) 500 mg twice daily, and hydroxy-chloroquine (HCQ) 200 mg daily (parallel triple therapy) vs sulfasalazine (SSZ) 40mg/kg/day in divided doses. After 3 months, (if DAS28 ≥3.2) methotrexate (MTX) 7.5 mg/week was added. After the maximum tolerated dose of MTX was reached, 400 mg/day of hydroxy-chloroquine (HCQ) was added	RCT Patients between 18 and 80 years of age who were newly diagnosed as having active rheumatoid arthritis (defined as symptom duration of <5 years, Disease Activity Score in 28 joints (DAS28) of >5.1) and who had not previously been treated with DMARDs other than hydroxychloroquine	N=96 1 year	Primary: Disease activity and functional outcome	Primary: After 12 months of follow-up, both groups demonstrated substantial improvements in the mean DAS28 score from baseline. The mean decrease in the DAS28 score was -4.0 (step-up therapy group) versus -3.3 (parallel therapy group; P=0.163). No significant differences in the percentages of patients with DAS28 remission (45% with step-up therapy group vs 33% parallel triple therapy group 33%), DAS28 good response (60% vs 41%, respectively) or American College of Rheumatology criteria for 20% improvement (ACR20; 77% vs 76%, respectively), ACR50 (60% vs 51%, respectively), or ACR70 (30% vs 20%, respectively) responses were seen. Improvements were seen in both groups in all disease activity variables, as well as in physical function and quality of life, but there were no significant differences between groups. There was no difference between the groups in radiologic progression over 12 months. Patients in both treatment groups reported adverse events with similar frequency. A total of 135 adverse events were reported in the step-up therapy group (48 gastrointestinal, 6 abnormal liver function tests, 27 infective, 16 mucocutaneous, 8 hematologic, 13 neurologic, and 17 other events). There were 141 adverse events reported in the parallel triple therapy group (52 gastrointestinal, 5 abnormal findings on liver function tests, 29 infective, 19 mucocutaneous, 8 hematologic, 6 neurologic, and 22 others).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in patients with persistent disease activity (step-up therapy)				
Treatment of Toxoplasmosis				
Dedicoat et al.[54] (2006) Pyrimethamine and clindamycin (P+C) vs pyrimethamine and sulfadiazine (P +S) vs sulfamethoxazole and trimethoprim (SMX-TMP)	MA Patients with the acquired immunodeficiency syndrome and toxoplasmosis	N=475 (3 trials) Variable duration	Primary : Mortality, clinical response to treatment, (neurological outcome, and serious adverse events) Secondary: Radiological response and minor adverse events	Primary: <u>P+C vs P+S</u> One of the trials showed complete or partial clinical response in 46.2% of the patients receiving P+C compared to 48.5% of the patients receiving P+S (RR 0.95; 95% CI: 0.55 to 1.64). The second trial was excluded due to lack of data. For both of the trials, the two treatment arms did not differ for death (RR 1.41; 95% CI: 0.88 to 2.28). <u>P+S vs SMX-TMP</u> Seventy percent of subjects in each group had a good clinical response. Secondary: Sixty-eight percent of patients in the SMX-TMP group compared to 62% in the P+S group had a good radiological outcome (RR 1.09; 95% CI: 0.78 to 1.51). Twelve percent of patients randomized to SMX-TMP and 22% patients randomized to P+S experienced an adverse event (RR 0.58; 95% CI: 0.21 to 1.61). There were no statistically significant differences between all of the treatment groups (SMX-TMP, P+C or P+S; RR 1.51; 95% CI: 0.86 to 2.67).

Study abbreviations: CI=confidence interval, DB=double-blind, HR=Hazard Ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PRO=prospective, RCT=randomized controlled trial, RR=relative risk

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 13. Relative Cost of the Antimalarials

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Artemether and lumefantrine	tablet	Coartem®	$$$	N/A
Atovaquone and proguanil	tablet	Malarone®*	$$$-$$$$	$$$-$$$$
Chloroquine	tablet	Aralen®*	$$$$	$$$
Hydroxychloroquine	tablet	Plaquenil®*	$$$$	$
Mefloquine	tablet	N/A	N/A	$$$
Primaquine	tablet	N/A	N/A	$$
Pyrimethamine	tablet	Daraprim®	$$$$	N/A
Quinine	capsule	Qualaquin®	$$$$	N/A

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

X. Conclusions

The antimalarials are approved for the prevention and treatment of malaria.[1-9] In the United States, most cases of malaria occur among individuals who traveled to endemic regions without receiving appropriate prophylactic therapy. Treatment for malaria should not be initiated until the diagnosis has been confirmed by laboratory investigations.[19] Once the diagnosis of malaria has been confirmed, appropriate antimalarial treatment must be initiated immediately. Treatment decisions are based upon the infecting *Plasmodium* species, the clinical status of the patient, and the drug susceptibility of the infecting parasites as determined by the geographic area where the infection was acquired.[19] Atovaquone/proguanil, chloroquine, hydroxychloroquine, mefloquine, and primaquine are available in a generic formulation.

In April 2011, the CDC published updated guidelines for the treatment of malaria based on drugs currently available in the United States.[20] For chloroquine-sensitive infections due to *P. falciparum*, *P. malariae and P. knowlesi*, initial treatment with chloroquine or hydroxychloroquine is recommended.[20] For the treatment of chloroquine-resistant infections due to *P. falciparum*, the CDC recommends the use of atovaquone/proguanil, artemether/lumefantrine or quinine (in combination with doxycycline, tetracycline or clindamycin) and does not give preference to one treatment regimen over another. Mefloquine is considered an alternative treatment option; however, due to higher rates of severe neuropsychiatric reactions seen at treatment doses, it is not recommended unless other options cannot be used.[20] For the treatment of chloroquine-resistant *P. vivax*, the CDC recommends the use of quinine (plus primaquine and doxycycline/tetracycline), atovaquone/proguanil (plus primaquine) or mefloquine (plus primaquine) and does not give preference to one treatment regimen over another.[20]

Chemoprophylaxis is recommended for individuals who will be traveling to areas where malaria transmission is expected. For travel to destinations where chloroquine-sensitive malaria is present, guidelines recommend the use of chloroquine, atovaquone/proguanil, doxycycline, mefloquine and primaquine (for travelers who are not G6PD-deficient).[21,70] For destinations where chloroquine-resistant malaria is present, chemoprophylaxis options are limited to atovaquone/proguanil, doxycycline and mefloquine.[21,70] Guidelines do not give preference to one chemoprophylactic agent over another.[21,70]

The agents in this class are also approved for the treatment of non-malarial diseases, including extraintestinal amebiasis (chloroquine), systemic lupus erythematosus and rheumatoid arthritis (hydroxychloroquine), as well as toxoplasmosis (pyrimethamine). Guidelines for the use of disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis recommend the use of hydroxychloroquine monotherapy for patients without poor prognostic features, with low disease activity, and with disease duration ≤24 months.[23] It is also recommended in combination with other DMARDs for patients with intermediate to high disease activity. For the treatment of systemic lupus erythematosus, hydroxychloroquine is recommended as one of several initial treatment options.[24] In patients with HIV infection, the recommended initial treatment for toxoplasmosis encephalitis consists of the combination of pyrimethamine, sulfadiazine and leucovorin.[25]

There is insufficient evidence to support that one brand antimalarial is more efficacious than another within its given indication. Since the antimalarials are not used for the management of common infectious diseases that would be seen in general use, formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand antimalarials 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 antimalarial 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiprotozoals, Miscellaneous
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I. Overview

The miscellaneous antiprotozoals are approved for the treatment of various infectious diseases, including amebiasis, anaerobic bacterial infections, bacterial vaginosis, cryptosporidiosis, giardiasis, *Pneumocystis* pneumonia and trichomoniasis.[1-11] Amebiasis is a parasitic infection caused by *Entamoeba histolytica* which may or may not be symptomatic and can remain latent in an infected person for several years.[12-14] While the most frequent clinical manifestations are gastrointestinal, the parasite can spread to extraintestinal sites resulting in liver abscesses and other complications. Cryptosporidiosis is a parasitic infection caused by *Cryptosporidium* which results in self-limiting diarrhea in immunocompetent persons, but may lead to potentially life-threatening complications in immunocompromised persons.[12,15] Giardiasis is a parasitic infection caused by *Giardia lamblia* which may result in acute self-limiting diarrhea or chronic diarrhea associated with malabsorption and weight loss.[12,16] All three parasitic infections can be transmitted from person-to-person, via the fecal-oral route, or by ingesting microbial cysts from contaminated food and water.[12-16]

Pneumocystis pneumonia (PCP) is caused by *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*), which is classified as a fungus, but also shares characteristics with protozoa.[17,20] *Pneumocystis* is commonly found in the lungs of healthy people and rarely causes disease. However, PCP is common among immunocompromised persons, including HIV-infected individuals, people taking immunosuppressant medications, as well as in those who have undergone bone marrow or solid organ transplantation.

Bacterial vaginosis results from replacement of the normal hydrogen peroxide-producing *Lactobacillus* species in the vagina with anaerobic bacteria.[19] Untreated vaginitis is associated with numerous health risks, such as pelvic inflammatory disease, cervicitis, postoperative infection, preterm delivery, postpartum endometritis, posthysterectomy infections, intrauterine infections and other sexually transmitted infections.[18] Trichomoniasis is caused by the protozoan *Trichomonas vaginalis* and is primarily a sexually transmitted disease.[19] However, the organism can survive for short periods of time on moist surfaces, such as bathing or toilet articles, and can be transmitted by nonsexual contact. Symptoms include vaginal discharge, odor, itching, dysuria and dyspareunia.

The miscellaneous antiprotozoals differ in their mechanism of action.[1-11] Atovaquone is thought to inhibit electron transport, which may lead to the inhibition of nucleic acid and ATP synthesis. Metronidazole and tinidazole are antiprotozoal and antibacterial agents. They are reduced by intracellular proteins, which produce free radicals that results in the death of the microorganism. The antiprotozoal activity of nitazoxanide is thought to be due to interference with the pyruvate:ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction, which is essential to anaerobic energy metabolism. Pentamidine interferes with protozoal nuclear metabolism by inhibition of DNA, RNA, phospholipid, and protein synthesis.

The miscellaneous antiprotozoals that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Metronidazole is the only product that is available in a generic formulation. This class was last reviewed in November 2009.

Table 1. Antiprotozoals, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Atovaquone	suspension	Mepron®	none
Metronidazole	capsule, injection, extended-release tablet, tablet	Flagyl®*, Flagyl ER®	metronidazole
Nitazoxanide	suspension, tablet	Alinia®	none
Pentamidine	inhalation, injection	Nebupent®, Pentam 300®	none
Tinidazole	tablet	Tindamax®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

The miscellaneous antiprotozoals 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 FDA-approved indications for the miscellaneous antiprotozoals 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 anti-infective 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 Antiprotozoals, Miscellaneous[1-11]

Organism	Atovaquone	Metronidazole	Nitazoxanide	Pentamidine	Tinidazole
Gram-Positive Anaerobes					
Clostridium species		✔			
Eubacterium species		✔			
Peptococcus niger		✔			
Peptostreptococcus species		✔			
Gram-Negative Anaerobes					
Bacteroides fragilis		✔			
Bacteroides distasonis		✔			
Bacteroides ovatus		✔			
Bacteroides thetaiotaomicron		✔			
Bacteroides vulgatus		✔			
Fusobacterium species		✔			
Protozoal Parasites					
Cryptosporidium parvum			✔		
Entamoeba histolytica		✔			✔
Giardia lamblia			✔		✔
Trichomonas vaginalis		✔			✔
Other Microorganisms					
Gardnerella vaginalis					✔
Haemophilus vaginalis					✔
Pneumocystis jiroveci	✔			✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Antiprotozoals, Miscellaneous

Clinical Guideline	Recommendation(s)
Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA): **Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults[25] (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 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

Clinical Guideline	Recommendation(s)
	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)**[104] **(2009)**	Treatment of *Clostridium difficile* infection (CDI)
	o 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**[105] **(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

Clinical Guideline	Recommendation(s)
	○ First-line: doxycycline or tetracycline ○ Alternative: azithromycin or ciprofloxacin • Shigellosis ○ First-line: ciprofloxacin ○ Alternative: pivmecillinam or ceftriaxone • Amebiasis ○ First-line: metronidazole • Giardiasis ○ First-line: metronidazole • *Campylobacter* ○ First-line: azithromycin
Infectious Diseases Society of America (IDSA): **The Practice of Travel Medicine[106] (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, and 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.
Centers for Disease Control and	<u>General recommendations</u>

Clinical Guideline	Recommendation(s)
Prevention (CDC): **Diagnosis and Management of Foodborne Illnesses: A Primer for Physicians and Other Health Care Professionals**[27] **(2004)**	• Oral rehydration therapy is indicated for patients with mild-to-moderate dehydration. Intravenous therapy may be required for severe dehydration. • Selection of an appropriate antimicrobial regimen relies on clinical presentation, the isolation of the responsible pathogen, and susceptibility testing. • Once the etiology of diarrhea has been identified via microbiological testing, antimicrobial therapy should be directed at that pathogen. • The routine use of antidiarrheal agents in infants and young children is not recommended due to potentially serious adverse effects. Cryptosporidium • Supportive care; symptoms are usually self-limiting. • If severe symptoms, consider paromomycin for 7 days. For children aged 1-11 years, consider nitazoxanide for 3 days. *Entamoeba histolytica* • The recommended treatment includes the combination of metronidazole and a luminal agent (iodoquinol or paromomycin). *Giardia lamblia* • The use of metronidazole is recommended.

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Management of Infectious Diarrhea**[26] **(2001)**	General Recommendations
	• Due to the risks of dehydration and malnutrition, guidelines recommend rehydration therapy as the initial management of patients with acute diarrheal illnesses.
	• Due to changing patterns of antimicrobial resistance, selection of antimicrobial regimens for empirical therapy should be based on prediction of the most likely pathogens(s) and knowledge of local susceptibility patterns.
	• Once the etiology of diarrhea has been identified via microbiological testing, antimicrobial therapy should be adjusted as necessary.
	Recommendations for Therapy Against Specific Pathogens
	• *Clostridium difficile*
	  ○ The offending antibiotic should be withdrawn if possible.
	  ○ Treatment with metronidazole 250 mg four times daily or 500 mg three times daily for 10 days is recommended.
	• *Entamoeba histolytica*
	  ○ The recommended treatment regimen includes metronidazole 750 mg three times daily for 5-10 days plus either diiodohydroxyquin 650 mg three times daily for 20 days or paromomycin 500 mg three times daily for 7 days.

Sanford Guide to Antimicrobial Therapy[89] **(2011)**	Amebiasis (*Entamoeba histolytica*)
	• Asymptomatic cyst passer:
	  ○ Primary: paromomycin 25-35 mg/kg/day in 3 divided doses for 7 days or iodoquinol* 650 mg 3 times daily for 20 days
	  ○ Alternative: diloxanide furoate* 500 mg 3 times daily for 10 days
	• Patient with diarrhea/dysentery (mild or moderate disease):
	  ○ Primary: metronidazole 500-750 mg orally 3 times daily for 10 days or tinidazole 2 g once daily for 3 days, followed by either paromomycin or iodoquinol* as above to clear intestinal cysts
	• Severe intestinal disease, hepatic abscess or other extraintestinal disease:
	  ○ Metronidazole 750 mg IV to oral 3 times daily for 10 days or tinidazole 2 g once daily for 5 days, followed by paromomycin to clear intestinal cysts

Clinical Guideline	Recommendation(s)
	Cryptosporidiosis (*Cryptosporidium hominis* or *C parvum*) • Immunocompetent/HIV-negative: nitazoxanide 500 mg orally twice daily for 3 days • HIV with immunodeficiency: effective antiretroviral therapy is the best therapy Giardiasis (*Giardia lamblia*) • Primary: tinidazole 2 g orally as a single dose or nitazoxanide 500 mg orally twice daily for 3 days • Alternative: albendazole 400 mg orally once daily for 5 days, metronidazole 250 mg orally three times daily for 5 days, mebendazole 200 mg orally three times daily for 5-7 days Bacterial Vaginosis • Primary: metronidazole 500 mg orally twice daily for 7 days, metronidazole vaginal gel once daily for 5 days, tinidazole 2 g orally once daily for 2 days, or tinidazole 1 g orally once daily for 5 days • Alternative: clindamycin 300 mg orally twice daily for 7 days or clindamycin ovules 100 mg intravaginally once daily for 3 days Trichomoniasis • Primary: metronidazole 2 g orally as a single dose, metronidazole 500 mg twice daily for 7 days, or tinidazole 2 g orally as a single dose
American College of Obstetricians and Gynecologists (ACOG): **Clinical Management Guidelines for Obstetrician-Gynecologists: Vaginitis[18] (2006)**	Bacterial Vaginosis • Recommended treatments: vaginal clindamycin, oral clindamycin, vaginal metronidazole, or oral metronidazole • The treatments seem to have comparable clinical efficacy and safety. • Oral metronidazole may be associated with significant gastrointestinal symptoms. • Disulfiram-like reactions may occur with both oral and topical metronidazole. Trichomoniasis • Recommended treatments: metronidazole 2 g as a single dose, metronidazole 500 mg twice daily for 7 days, or tinidazole 2 g as a single dose • Although metronidazole has been the mainstay of treatment in the United States, tinidazole also has recently been approved as single-dose therapy. Both treatments seem to be equally efficacious. • Side effects seem to be of similar nature, including a possible disulfiram-like effect; alcohol should be avoided for 24 hours after metronidazole use and 72 hours after tinidazole use. • Partners of women with trichomoniasis also should be treated.
British Association for Sexual Health and HIV (BASHH): **National Guideline for the Management of Bacterial Vaginosis[28] (2006)**	• Recommended regimens: metronidazole 400-500 mg orally twice daily for 5-7 days or metronidazole 2 g orally as a single dose • Alternative regimens: intravaginal metronidazole gel (0.75%) once daily for 5 days, intravaginal clindamycin cream (2%) once daily for 7 days, or clindamycin 300 mg twice daily for 7 days • All these treatments have been shown to achieve cure rates of 70-80% after 4 weeks in controlled trials using placebo or comparison with oral metronidazole. Oral metronidazole treatment is established and usually well tolerated. Dosage and duration used in trials have varied from 400 mg twice daily for 5 days to 500 mg twice daily for 7 days. The 2 g immediate dose may be slightly less effective at 4 week follow up. • Intravaginal metronidazole gel and clindamycin cream have similar efficacy. Theoretically, metronidazole has an advantage because it is less active against lactobacilli than clindamycin. Conversely, clindamycin is more active than metronidazole against most of the

Clinical Guideline	Recommendation(s)
	bacteria associated with BV.
British Association for Sexual Health and HIV (BASHH): **National Guideline on the Management of *Trichomoniasis vaginalis*[29] (2007)**	• Recommended regimens: metronidazole 2g orally in a single dose or metronidazole 400-500 mg twice daily for 5-7 days • Alternative regimen: tinidazole 2g orally in a single dose • Metronidazole and tinidazole have both demonstrated similar clinical efficacy.

Centers for Disease Control and Prevention (CDC): **Sexually Transmitted Diseases Treatment Guidelines[19] (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>Recurrent and Persistent Urethritis</u>
	• Recommended regimen: metronidazole 2 g daily once or tinidazole 2 g daily once, plus azithromycin 1 g once.
	<u>Sexual Assault and STDs</u>
	• Recommended regimen: ceftriaxone plus metronidazole plus azithromycin or doxycycline
	<u>Trichomoniasis</u>
	• Recommended regimens: metronidazole 2 g orally in a single dose or tinidazole 2 g orally in a single dose
	• Alternative regimen: metronidazole 500 mg orally twice a day for 7 days
	<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 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

Clinical Guideline	Recommendation(s)

World Health Organization (WHO): **Guidelines for the Management of Sexually Transmitted Infections[21] (2003)**	<u>Bacterial Vaginosis</u>
	• The recommended treatment is metronidazole orally for 7 days.
	• Alternative regimens include oral metronidazole as a single dose, clindamycin vaginal cream for 7 days, metronidazole vaginal gel for 7 days, or oral clindamycin.
	• Pregnant patients should be treated with oral metronidazole after the first trimester. If treatment is necessary during the first trimester, metronidazole as a single dose may be given. Alternative regimens include oral clindamycin or metronidazole vaginal gel.
	<u>Pelvic Inflammatory Disease</u>
	• Outpatient treatment includes single-dose therapy for uncomplicated gonorrhea plus doxycycline and metronidazole.
	• Inpatient treatment includes:
	  ○ Ceftriaxone, plus doxycycline, plus metronidazole or chloramphenicol OR
	  ○ Clindamycin plus gentamicin OR
	  ○ Ciprofloxacin or spectinomycin, plus doxycycline or tetracycline, plus metronidazole or chloramphenicol
	<u>Trichomoniasis</u>
	• Vaginal infections may be treated with metronidazole or tinidazole orally as a single dose. Alternatives include metronidazole for 7 days or tinidazole for 5 days.
	• Patients not cured with repeated courses of metronidazole may be treated with metronidazole orally as a single dose plus metronidazole vaginally for 3-7 days.
	• Urethral infections may be treated with metronidazole for 7 days or tinidazole for 5 days.
	• Neonatal infections should be treated with oral metronidazole for 5 days.

Infectious Diseases Society of America (IDSA): **Guidelines for the Selection of Anti-Infective Agents for Complicated Intra-abdominal Infections[22] (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,

Clinical Guideline	Recommendation(s)
	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> • 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.

Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections**[23] **(2005)**	<u>Animal Bites</u>
	• Oral treatment options
	  ○ Amoxicillin/clavulanate is recommended.
	  ○ Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin.
	  ○ Other options, including fluoroquinolones, trimethoprim-

Clinical Guideline	Recommendation(s)

	sulfamethoxazole, and cefuroxime, may require an additional agent active against anaerobes, such as metronidazole or clindamycin.
	  ○ 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
	  ○ β-lactam/β-lactamase combinations, piperacillin/tazobactam, second-generation cephalosporins, and carbapenems.
	  ○ 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 (e.g., moxifloxacin and gatifloxacin) plus clindamycin, or trimethoprim-sulfamethoxazole plus metronidazole may be useful.
	<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 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.

Surgical Infection Prevention Guideline Writers Workgroup (SIPGWW): **Antimicrobial**	<u>Colorectal Surgery</u> • Antimicrobial prophylaxis for colorectal operations can consist of an orally administered antimicrobial bowel preparation, a preoperative

Clinical Guideline	Recommendation(s)
Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project[24] (2004)	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. Gynecologic and Obstetrical Surgery • For abdominal or vaginal hysterectomy, cefotetan is preferred, but reasonable alternatives are cefazolin and cefoxitin. • Metronidazole monotherapy is included in the American College of Obstetricians and Gynecologists Practice Bulletin as an alternative for patients undergoing hysterectomy, although it may be less effective as a single agent for prophylaxis. • 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.
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[20] (2008)**	Cryptosporidiosis • In the setting of severe immunosuppression, ART with immune restoration to a CD4+ count >100 cells/µL leads to resolution of clinical cryptosporidiosis and is the mainstay of treatment. • All patients with cryptosporidiosis should be offered ART as part of the initial management of their infection. • Management should include symptomatic treatment of diarrhea. Rehydration and repletion of electrolyte losses by either the oral or IV route are important. Severe diarrhea can exceed >10 L/day among patients with AIDS, often requiring intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions. Primary Prophylaxis of *Pneumocystis* Pneumonia (PCP) • Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic agent. • If TMP-SMX cannot be tolerated, prophylactic regimens that can be recommended as alternatives include dapsone, dapsone plus pyrimethamine plus leucovorin, aerosolized pentamidine administered by the Respirgard II nebulizer, and atovaquone. Atovaquone is as effective as aerosolized pentamidine or dapsone. For patients seropositive for *Toxoplasma gondii* who cannot tolerate TMP-SMX, recommended alternatives to TMP-SMX for prophylaxis against both PCP and toxoplasmosis include dapsone plus pyrimethamine plus leucovorin or atovaquone with or without pyrimethamine plus leucovorin. Treatment of *Pneumocystis* Pneumonia (PCP) • TMP-SMX is the treatment of choice. • Alternative therapeutic regimens for mild-to-moderate disease include dapsone and TMP, primaquine plus clindamycin, and atovaquone (this is less effective than TMP-SMX for mild-to-moderate disease but has fewer side effects). • Alternative therapeutic regimens for patients with moderate-to-severe disease include clindamycin-primaquine or intravenous (IV) pentamidine (generally the drug of second choice for severe disease). Aerosolized pentamidine should not be used for the treatment of PCP because of limited efficacy and more frequent relapse.

Clinical Guideline	Recommendation(s)
	• The recommended duration of therapy for PCP is 21 days. • Patients who have a history of PCP should be administered chemoprophylaxis for life with TMP-SMX unless immune reconstitution occurs as a result of ART. For patients who are intolerant of TMP-SMX, alternatives include dapsone, dapsone plus pyrimethamine, atovaquone, or aerosolized pentamidine. Primary Prophylaxis of *Toxoplasma* Encephalitis (TE) • TMP-SMX is the recommended prophylactic agent. • 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. 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.

*Product is not commercially available in the United States.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antiprotozoals 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 Antiprotozoals, Miscellaneous[1-11]

Indication	Atovaquone	Metronidazole	Nitazoxanide	Pentamidine	Tinidazole
Acute intestinal amebiasis (amebic dysentery)		✔			✔
Amebic liver abscess		✔			✔
Bacterial septicemia		✔			
Bacterial vaginosis		✔ §			✔
Bone and joint infections		✔			
Central nervous system infections		✔			
Diarrhea caused by *Cryptosporidium parvum* or *Giardia lamblia*			✔		
Endocarditis		✔			
Giardiasis					✔
Gynecologic infections		✔			
Intra-abdominal infections		✔			
Lower respiratory tract infections		✔			
Perioperative prophylaxis, contaminated or potentially contaminated colorectal surgery		✔ ‡			
Skin and skin-structure infections		✔			
Prevention of *Pneumocystis carinii* pneumonia in high-risk, HIV-infected patients				✔ †	
Prevention of *Pneumocystis carinii* pneumonia in patients who are intolerant to trimethoprim-sulfamethoxazole	✔				
Treatment of mild-to-moderate *Pneumocystis carinii* pneumonia in patients who are intolerant to trimethoprim-sulfamethoxazole	✔				
Treatment of *Pneumocystis carinii* pneumonia				✔ ‡	
Trichomoniasis		✔			✔

†Inhalation formulation only
‡Intravenous formulation only
§Extended-release formulation only

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antiprotozoals are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Antiprotozoals, Miscellaneous[1-11]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (Hours)
Atovaquone	47	99.9	Limited	Feces (>94)	67-78
Metronidazole	100	<20	Liver	Renal (60-80) Feces (6-15)	6-14
Nitazoxanide	70	>99	Conjugation	Renal (33) Feces (67)	1-1.6
Pentamidine	Not reported	69	Not reported	Renal (12)	6-9
Tinidazole	100	12	Liver	Renal (20-25) Feces (12)	12-14

V. Drug Interactions

Significant drug interactions with the miscellaneous antiprotozoals are listed in Table 6.

Table 6. Significant Drug Interactions with the Antiprotozoals, Miscellaneous[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Metronidazole, tinidazole	1	Anticoagulants	The anticoagulant effect of warfarin may be enhanced; hemorrhage could occur. Liver metabolism of the S (−) enantiomorph of racemic warfarin may be decreased by metronidazole.
Metronidazole, tinidazole	1	Busulfan	Busulfan trough concentrations may be elevated, increasing the risk of serious toxicity (e.g., veno-occlusive disease, hemorrhagic cystitis).
Metronidazole, tinidazole	1	Disulfiram	Acute toxic psychosis may occur during the coadministration of metronidazole and disulfiram.
Metronidazole	1	Ergot alkaloids	Plasma concentrations and pharmacologic effects of ergot alkaloids may be increased by metronidazole. The potential for the development of ergotism exists.
Pentamidine injection	1	Class III antiarrhythmics	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when class III antiarrhythmics are co-administered with pentamidine.
Pentamidine injection	1	Dofetilide	The risk of cardiovascular toxicity, including torsade de pointes, may be increased by co-administration of pentamidine and dofetilide.

Generic Name(s)	Significance Level	Interaction	Mechanism
Pentamidine injection	1	H1-antagonists	Co-administration of pentamidine and H1-antagonists may cause cardiovascular toxicity, including excessive prolongation of the QT interval and, rarely, fatal cardiac arrhythmias (torsades de pointes).
Pentamidine	1	Nilotinib, vandetanib	Additive QT prolongation may occur during coadministration of nilotinib or vandetanib and pentamidine.
Pentamidine	1	QTC-prolonging agents	Additive QT prolongation may occur during coadministration with pentamidine.
Pentamidine inhalation	1	Toremifene	Additive QT prolongation may occur during coadministration of toremifene and pentamidine.
Tinidazole	1	Cyclosporine	Tinidazole may increase plasma concentrations and pharmacologic effects of cyclosporine. Renal toxicity possibly associated with elevated cyclosporine blood or plasma concentrations may occur.
Tinidazole	1	H-1 antagonists	Tinidazole may decrease the hepatic metabolism of H-1 antagonists. Elevated H-1 antagonists plasma concentrations with severe cardiac toxicity may occur.
Atovaquone	2	Rifamycins	Plasma concentrations of atovaquone may be decreased by rifamycins.
Atovaquone	2	Tetracyclines	Tetracyclines may decrease the plasma concentrations and pharmacologic effects of atovaquone.
Metronidazole, tinidazole	2	Barbiturates	Therapeutic failure of metronidazole may occur by means of barbiturate induction of metronidazole metabolism, resulting in more rapid elimination and lower serum concentrations.
Metronidazole, tinidazole	2	Macrolide immunosuppressants	Pharmacologic and toxic effects of macrolide immunosuppressants may be increased by metronidazole. Elevated plasma concentrations of macrolide immunosuppressants with nephrotoxicity may occur.
Metronidazole, tinidazole	2	Protease inhibitors	Co-administration of metronidazole and HIV protease

Generic Name(s)	Significance Level	Interaction	Mechanism
			inhibitors may cause an alcohol intolerance reaction.
Pentamidine injection	2	Flecainide	Additive QT interval prolongation may occur during coadministration of pentamidine and flecainide.
Pentamidine injection	2	Lapatinib	Additive QT interval prolongation is listed in the manufacturer's package labeling for lapatinib as a possibility when lapatinib and pentamidine are co-administered.
Pentamidine injection	2	Perflutren	Additive QT interval prolongation may occur during coadministration of perflutren and pentamidine.
Pentamidine injection	2	Propafenone	Additive QT interval prolongation may occur during coadministration of pentamidine and propafenone.
Pentamidine injection	2	Tetrabenazine	Additive QT prolongation may occur during coadministration of tetrabenazine and pentamidine.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antiprotozoals are listed in Table 7. The boxed warning for metronidazole is listed in Table 8. The boxed warning for tinidazole is listed in Table 9.

Table 7. Adverse Drug Events (%) Reported with the Antiprotozoals, Miscellaneous[1-11]

Adverse Events	Atovaquone	Metronidazole	Nitazoxanide	Pentamidine	Tinidazole
Cardiovascular					
Cardiac arrhythmias	-	-	-	✔	-
Chest pain	-	-	-	✔	-
Hypertension	-	-	<1	✔	-
Hypotension	<1	-	-	5	-
Palpitations	-	-	-	✔	✔
Syncope	-	✔	<1	✔	-
T-wave flattening	-	✔	-	-	-
Tachycardia	-	-	<1	✔	-
Torsades de pointes	-	-	-	✔	-
Sinus arrhythmia	✔	-	-	-	-
Central Nervous System					
Anxiety	≤7	-	-	✔	-
Aseptic meningitis	-	✔	-	-	-
Asthenia	≤22	✔	<1	-	✔
Ataxia	-	✔	-	-	✔
Coma	-	-	-	-	✔
Confusion	-	✔	-	2	✔
Convulsions	-	✔	-	-	✔
Dementia	✔	-	-	-	-
Depression	✔	✔	-	✔	✔

Adverse Events	Atovaquone	Metronidazole	Nitazoxanide	Pentamidine	Tinidazole
Dizziness	≤8	✔	<1	✔	2
Drowsiness	-	-	<1	✔	✔
Encephalopathy	-	✔	-	-	-
Fatigue	-	✔	-	✔	2
Fever	14-40	✔	<1	✔	✔
Giddiness	-	-	-	-	✔
Hallucinations	-	-	-	2	-
Headache	16-31	✔	3	✔	1
Hearing loss	-	✔	-	-	-
Hypesthesia	-	-	<1	-	-
Insomnia	10-19	✔	<1	✔	✔
Irritability	-	✔	-	-	-
Malaise	-	✔	-	✔	2
Peripheral neuropathy	≤22	✔	<1	-	✔
Seizure	-	-	-	✔	-
Tremor	-	-	<1	✔	-
Vertigo	-	✔	-	✔	✔
Weakness	-	✔	-	✔	2
Dermatological					
Burning sensation	-	-	-	-	✔
Erythema multiforme	✔	-	-	-	-
Pruritus	5-10	✔	<1	✔	✔
Rash	22-46	✔	<1	3	✔
Stevens-Johnson syndrome	✔	✔	-	-	-
Sweating	>10	-	-	-	✔
Urticaria	✔	✔	-	✔	✔
Gastrointestinal					
Abdominal pain	4-21	✔	7	✔	✔
Appetite decreased	7	✔	<1	6	2
Appetite increased	✔	-	-	-	-
Colitis	-	-	-	✔	-
Constipation	3	✔	<1	-	<1
Cramps	5	✔	<1	✔	2
Diarrhea	19-42	✔	4	✔	✔
Dry mouth	-	✔	<1	✔	✔
Dyspepsia	5	✔	<1	✔	2
Epigastric distress	5	✔	<1	✔	2
Esophagitis	-	-	-	✔	-
Flatulence	-	-	<1	-	-
Glossitis	-	✔	-	-	✔
Hematochezia	-	-	-	✔	-
Nausea	21-32	12	3	6	3
Pseudomembranous colitis	-	✔	-	-	-
Salivation	-	-	-	✔	✔
Stomatitis	-	✔	-	-	✔
Taste perversion	3	✔	-	2	4
Thirst	-	-	<1	-	✔
Tongue discoloration	-	-	-	-	✔
Vomiting	14-22	✔	<1	✔	2
Genitourinary					
Impaired renal function	✔	-	-	29	-
Azotemia	-	-	-	9	-
Cystitis	-	✔	-	-	-
Dryness of vagina	-	✔	-	-	-

Adverse Events	Atovaquone	Metronidazole	Nitazoxanide	Pentamidine	Tinidazole
Dyspareunia	-	✔	-	-	-
Dysuria	-	✔	<1	-	-
Incontinence	-	✔	-	-	-
Libido decrease	-	✔	-	-	-
Menstrual irregularities	-	✔	<1	-	-
Polyuria	-	✔	-	-	-
Proctitis	-	✔	-	-	-
Sense of pelvic pressure	-	✔	-	-	-
Urethral discomfort	-	✔	-	-	-
Urine discoloration	-	✔	<1	-	✔
Vaginal discharge	-	-	-	-	✔
Vulvovaginal candidiasis	-	✔	-	-	-
Hematologic					
Anemia	4-6	-	<1	1	-
Bone marrow aplasia	-	✔	-	-	-
Eosinophilia	-	-	-	✔	-
Leukocytosis	-	-	<1	-	-
Leukopenia	-	✔	-	10	✔
Methemoglobinemia	✔	-	-	-	-
Neutropenia	3-5	✔	-	✔	✔
Pancytopenia	-	-	-	✔	-
Thrombocytopenia	✔	✔	-	3	✔
Hepatic					
Alkaline phosphatase increase	8	-	-	-	-
ALT increased	6	-	-	-	✔
AST increased	4	-	-	-	✔
Bilirubin increased	✔	-	-	-	-
Liver function tests abnormal	-	-	-	9	-
Laboratory Test Abnormalities					
Amylase increased	7-8	-	-	-	-
BUN increased	<1	-	-	7	-
Hypercalcemia	-	-	-	✔	-
Hyperglycemia	9	-	-	✔	-
Hypoglycemia	<1	-	-	6	-
Hyponatremia	7-10	-	-	-	-
Serum creatinine increased	<1	-	-	24	-
SGPT increased	-	-	<1	-	-
Musculoskeletal					
Arthralgias	-	-	-	-	✔
Arthritis	-	-	-	-	✔
Bone fracture	-	-	<1	-	-
Joint pain	-	✔	-	-	-
Leg cramps	-	-	<1	-	-
Myalgias	-	-	<1	-	✔
Pain	≤10	-	<1	-	-
Respiratory					
Bronchitis	-	-	-	✔	-
Bronchospasm	2-4	-	-	-	✔
Cough	14-25	-	-	✔	-
Dyspnea	15-21	-	-	✔	✔
Epistaxis	-	-	<1	-	-
Nasal congestion	-	✔	-	-	-
Pharyngitis	-	✔	<1	✔	✔
Rhinitis	5-24	✔	-	-	-

Adverse Events	Atovaquone	Metronidazole	Nitazoxanide	Pentamidine	Tinidazole
Sinusitis	7-10	✔	-	✔	-
Tachypnea	-	-	-	✔	-
Upper respiratory tract infections	-	✔	-	✔	-
Wheezing	-	-	-	✔	-
Special Senses					
Ear ache	-	-	<1	-	-
Eye discoloration	-	-	<1	-	-
Tinnitus	-	✔	-	-	-
Vision abnormalities	-	-	-	✔	-
Other					
Allergic reaction	1	-	<1	-	-
Anaphylaxis	-	-	-	✔	-
Angioedema	✔	-	-	-	✔
Candidiasis	5-10	✔	-	✔	✔
Diabetes mellitus	-	-	-	✔	-
Flu-like syndrome	>10	-	<1	-	-
Flushing	-	✔	-	-	✔
Herpes zoster	-	-	-	✔	-
Infection	18-22	✔	-	✔	-
Infiltration	-	-	-	✔	-
Injection site reaction	-	-	-	11	-
Ketoacidosis	-	-	-	✔	-
Night sweats	-	-	-	✔	-
Non-specific herpes	-	-	-	✔	-
Non-specific influenza	-	✔	-	✔	-
Pancreatitis	✔	✔	-	✔	-
SIADH	-	-	-	✔	-
Thrombophlebitis	-	✔	-	-	-
Vortex keratopathy	✔	-	-	-	-

✔ Percent not specified
- Event not reported

Table 8. 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 9. Boxed Warning for Tinidazole[1]

WARNING
Carcinogenicity has been seen in mice and rats treated chronically with metronidazole, another nitroimidazole agent. Although such data have not been reported for tinidazole, the 2 drugs are structurally related and have similar biologic effects. Reserve its use only for the conditions for which it is indicated.

VII. Dosing and Administration

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

Table 10. Usual Dosing Regimens for the Antiprotozoals, Miscellaneous[1-11]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Atovaquone	Prevention of PCP: 1,500 mg once daily with a meal Treatment of Mild-to-Moderate PCP: 750 mg BID for 21 days	Prevention of PCP: 13-16 years of age: 1,500 mg once daily with a meal Treatment of Mild-to-Moderate PCP: 750 mg BID for 21 days	Suspension: 750 mg/5 ml
Metronidazole	Acute Intestinal Amebiasis: 750gm TID for 5-10 days Amebic Liver Abscess: 500-750 mg TID for 5-10 days Anaerobic Bacterial Infections: Oral: 750 mg/kg every 6 hours for 7-10 days Intravenous: 15 mg/kg IV loading dose, followed by 7.5 mg/kg IV every 6 hours Bacterial Vaginosis: 750 mg once daily (extended-release tablets) for 7 days Perioperative Prophylaxis: 15 mg/kg IV one hour prior to procedure and if necessary, 7.5 mg/kg IV at 6 and 12 hours after the initial dose Trichomoniasis: Females: 1-day regimen: 2 g as a single dose or 2 divided doses of 1 g each given in the same day 7-day regimen: 250 mg TID for 7 days or 375 mg BID for 7 days Males: Treatment should be individualized.	Amebiasis: Capsule: 35-50 mg/kg per 24 hours, divided into 3 doses, orally for 10 days	Capsule: 375 mg Injection: 500 mg/500 ml Tablet (IR): 250 mg 500 mg Tablet (ER): 750 mg
Nitazoxanide	Diarrhea Caused by *Giardia lamblia* or *Cryptosporidium parvum*: 500 mg every 12 hours for 3 days	Diarrhea Caused by *Giardia lamblia* or *Cryptosporidium parvum*: 1-3 years: 100 mg every 12 hours for 3 days 4-11 years: 200 mg every 12 hours for 3 days	Suspension: 100 mg/5 ml Tablet: 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		>12 years: 500 mg every 12 hours for 3 days	
Pentamidine	Prevention of PCP: Inhalation: 300 mg once every 4 weeks Treatment of PCP: Injection: 4 mg/kg IV/IM once daily for 14-21 days	Treatment of PCP: ≥4 months of age: Injection: 4 mg/kg IV/IM once daily for 14-21 days	Inhalation: 300 mg Injection: 300 mg
Tinidazole	Acute Intestinal Amebiasis: 2 g as a single dose for 3 days Amebic Liver Abscess: 2 g as a single dose for 3-5 days Bacterial Vaginosis: 2 g once daily for 2 days or 1 g once daily for 5 days Giardiasis: 2 g as a single dose Trichomoniasis: 2 g as a single dose; treat sexual partners with same dose and at the same time	Acute Intestinal Amebiasis: ≥3 years of age: 50 mg/kg/day as a single dose (up to 2 g per day) for 3 days Amebic Liver Abscess: ≥3 years of age: 50 mg/kg/day as a single dose (up to 2 g per day) for 3-5 days Giardiasis: ≥3 years of age: 50 mg/kg as a single dose (up to 2 g)	Tablet: 250 mg 500 mg

BID=two times daily, IV=intravenous, PO=by mouth, QD=once daily, QID=four times daily, TID=three times daily

VIII. Effectiveness

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

Table 11. Comparative Clinical Trials with the Antiprotozoals, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amebiasis				
Kokhani et al.[39] (1977) Metronidazole 2 g per day for 2 days vs tinidazole 2 g per day for 2 days	RCT Patients with amebic liver abscess	N=19 30 days	Primary: Efficacy rate	Primary: Efficacy rates were reported to be 56% and 100% in the metronidazole and tinidazole groups, respectively (P<0.05).
Mathur et al.[40] (1977) Metronidazole 2 g per day for 2 days vs tinidazole 2 g per day for 2 days	RCT Adult patients with amebic liver abscess (India)	N=22 30 days	Primary: Efficacy rate	Primary: Efficacy rates were reported to be 91% and 100% in the metronidazole and tinidazole groups, respectively (P=NS).
Misra et al.[81] (1977) Metronidazole 2 g per day for 3 days vs tinidazole 2 g per day for 3 days	RCT Patients with symptomatic intestinal amebiasis	N=60 30 days	Primary: Cure rates (relief of symptoms, healing of colonic ulcers and absence of *E histolytica* in stools and sigmoidoscopic scrapings), adverse events	Primary: After 30 days, cure rates were 53.3% and 90.0% in the metronidazole and tinidazole groups, respectively (P<0.01). The most frequently reported adverse events were gastrointestinal and were experienced in 53.3% and 26.7% of patients receiving metronidazole and tinidazole, respectively (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Baksih et al.[30] (1978) Metronidazole 2 g per day for 3 days vs tinidazole 2 g per day for 3 days	RCT Patients diagnosed with symptomatic intestinal amebiasis	N=257 30 days	Primary: Cure rate, adverse events	Primary: Cure rate was reported in 53.7% and 91.8% of patients in the metronidazole and tinidazole treatment groups, respectively (P<0.001). Overall, adverse events were reported in 54.4% and 31.3% of patients receiving metronidazole and tinidazole, respectively (P<0.01). The most frequently reported side effects with metronidazole were nausea (43.1%), anorexia (27.6%), vomiting (11.4%) and abdominal pain (11.4%). The most frequently reported side effects with tinidazole were bitter taste (14.9%), nausea (10.4%) and anorexia (8.2%).
Swami et al.[31] (1977) Metronidazole 2 g per day for 3 days vs tinidazole 2 g per day for 3 days	PG, RCT Patients diagnosed with symptomatic intestinal amebiasis and *E histolytica* present in stools (India)	N=56 30 days	Primary: Cure rate, adverse events	Primary: Cure rates were reported in 55.5% and 96.5% of patients in the metronidazole and tinidazole treatment groups, respectively (P<0.01). Overall, adverse events were reported in 37.0% and 51.7% of patients receiving metronidazole and tinidazole, respectively. Of patients reporting side effects, 8 of 10 patients and 2 of 15 patients reported the side effects to be of moderate severity with metronidazole and tinidazole, respectively. The most frequently reported side effects with metronidazole were nausea (21.2%), abdominal pain (12.1%) and colored urine (12.1%). The most frequently reported side effects with tinidazole were metallic taste (40.9%) and bitter taste (18.2%).
Singh et al.[32] (1977) Metronidazole 2 g per day for 3 days vs tinidazole 2 g per day for 3 days	RCT Patients diagnosed with symptomatic intestinal amebiasis and *E histolytica* present in stools (India)	N=56 30 days	Primary: Cure rate, adverse events	Primary: Combined clinical and parasitological cure rate was reported in 58.6% and 92.6% of patients in the metronidazole and tinidazole treatment groups, respectively (P<0.01). The most frequently reported adverse events were gastrointestinal and were experienced in 75.9% and 51.9% of patients receiving metronidazole and tinidazole, respectively.
Scragg et al.[34] (1977)	RCT Patients with	N=31 7 days	Primary: Success rates	Primary: Success rates were reported as 80% with metronidazole for an average of 7 days and 93.8% with tinidazole for an average of 4 days.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metronidazole 2 g for 3 days vs tinidazole 2 g for 3 days	amebic liver abscess			
Kundu et al.[36] (1977) Metronidazole 2 g per day for 3 days vs tinidazole 2 g per day for 3 days	RCT Patients with amebic liver abscesses	N=18 30 days	Primary: Cure rate, adverse events	Primary: Marked improvement within 1 week or after 1 week, followed by clinical cure by day 30 with no other specific treatment required was reported in 33.3% and 88.9% of patients in the metronidazole and tinidazole treatment groups, respectively (P<0.05). Mild gastrointestinal side effects were reported in 44.4% and 11.1% of patients receiving metronidazole and tinidazole, respectively. Two patients died, 1 in the metronidazole group due to adrenal insufficiency and 1 in the tinidazole group due to hepatic coma. Neither death was considered drug related.
Islam et al.[38] (1978) Metronidazole 2 g per day for 3-10 days vs tinidazole 2 g per day for 3-6 days	RCT Patients with amebic liver abscess	N=31 30 days	Primary: Efficacy rate	Primary: Efficacy rates were reported to be 80% and 93% in the metronidazole and tinidazole groups, respectively (P<0.05).
Simjee et al.[35] (1985) Metronidazole 2 g per day for 5 days vs	RCT Patients with amebic liver abscesses	N=48 8 weeks	Primary: Clinical cure, adverse events	Primary: Cure rate was reported in 100% of patients in both the metronidazole and tinidazole treatment groups (P=NS), although 7.4% and 19.0% of patients in the metronidazole and tinidazole treatment groups, respectively, required a second course of treatment. The most frequently reported adverse event was oral candidiasis and it was observed in 7.4% and 9.5% of patients receiving metronidazole and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tinidazole 2 g per day for 5 days A second course of the same study drug could be given if the patient showed no improvement after 5 days.				tinidazole, respectively.
Mendis et al.[37] (1984) Metronidazole 400 mg TID for 5 days vs tinidazole 2 g per day for 3 days	DB, RCT Patients with amebic liver abscess	N=34 30 days	Primary: Efficacy rate	Primary: Efficacy rates were reported to be 33% and 81% in the metronidazole and tinidazole groups, respectively (P<0.01).
Simjee et al.[101] (1985) Metronidazole 2 g daily for 5 days vs tindazole 2 g daily for 5 days Treatment was repeated after 5 days if there was no improvement.	PRO, PG Patients with uncomplicated amebic liver abscess in South Africa	N=48 8 weeks	Primary: Time to pain disappearance, time for temperature to settle, time for tenderness to disappear	Primary: Two patients treated with metronidazole and four patients treated with tinidazole required a second course of therapy. There was no difference between metronidazole or tinidazole in the time for pain to disappear (4.2 days vs 5.2 days, respectively); time for temperature to “settle” (5.2 days vs 5.2 days, respectively); or time for tenderness to disappear (7.9 vs 7.9 days, respectively).
Bassily et al.[33] (1987)	RCT Patients diagnosed	N=53 3 weeks	Primary: Microbiological cure	Primary: Microbiological cure rates at 3 weeks were 88% with metronidazole, 67% with tinidazole and 94% with ornidazole (P=0.0438).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metronidazole 1.5 g daily for 10 days vs tinidazole 1.5 g daily for 10 days vs ornidazole* 1 g daily for 10 days	with *E histolytica* intestinal infection			
Gonzales et al.[78] (2009) Metronidazole vs tinidazole vs other amebic therapies vs placebo	MA Adults and children with clinical symptoms of amoebic colitis	N=4,487 (37 trials) Variable duration	Primary: Clinical and parasitological failures, relapse, adverse events	Primary: <u>Tinidazole versus metronidazole (9 trials)</u> Tinidazole reduced clinical failure by 72% compared with metronidazole (RR 0.28, 95% CI 0.15 to 0.51). Results for parasitological failure did not show that tinidazole was more effective in eradicating *E. histolytica* compared to metronidazole. No data on relapse were reported. There were no serious adverse events or adverse events that necessitated drug withdrawal in the three trials that reported on this. For the other adverse events, they were more common in those given metronidazole compared to those given tinidazole (RR 0.65, 95% CI 0.46 to 0.92). The most common adverse events reported were nausea, vomiting, decreased appetite, altered taste or metallic taste, and abdominal discomfort. <u>Other drugs versus metronidazole (5 trials)</u> Other alternative drugs tested were ornidazole, panidazole, and satranidazole. The number of trials was too small to detect any difference in clinical failure or parasitological failure compared with metronidazole. For relapse, data were reported for two trials, and both compared ornidazole with metronidazole. There were more relapses in those given ornidazole compared with metronidazole (RR 4.74, 95% CI 1.07 to 20.99),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				but there were insufficient data to draw definite conclusions. There were no serious adverse events or withdrawals resulting from adverse events in two trials that reported on this. <u>Combination regimen versus metronidazole alone (3 trials)</u> Combination therapy reduced clinical failure one to 14 days after the end of treatment by 67% compared to monotherapy with metronidazole (RR 0.33, 95% CI 0.11 to 0.98). The combinations included dehydroemetine, tetracycline, and diloxanide furoate; a fixed-drug combination suspension of metronidazole and furazolidone; and a fixed-drug combination tablet of metronidazole and diiodohydroxyquinoline. For parasitological failure, results showed a 64% reduction in parasitological failures one to 14 days after the end of treatment in those given the combination compared to metronidazole alone (RR 0.36, 95% CI 0.15 to 0.86). Only one trial reported details for adverse events. One participant given a fixed-drug combination tablet of metronidazole and diiodohydroxyquinoline developed an unspecified allergic reaction on the first day necessitating withdrawal from the trial.
Bacterial Vaginosis				
Brandt et al.[80] (2008) Metronidazole 2,000 mg orally as a single dose vs metronidazole 1,000 mg intravaginally once daily for 2 days	RCT, DB, PC, MC Patients ≥18 years of age with bacterial vaginosis	N=263 12 weeks	Primary: Cure of bacterial vaginosis and recurrence Secondary: Adverse events and tolerability	Primary: The cure rate in patients treated with intravaginal metronidazole was slightly higher compared to patients treated with oral metronidazole (92.5% vs 89.9%), however there was no significant difference between the treatment groups. Recurrences occurred in 10.0% of patients receiving oral metronidazole and 13.9% of patients receiving intravaginal metronidazole. There was no statistical significant difference between the groups Secondary: The physician's rating of the overall tolerability was better with intravaginal metronidazole compared to oral metronidazole (P=0.048). The patients' overall satisfaction with the intravaginal administration of metronidazole was higher as compared to the oral administration

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.046). Significantly more adverse events were reported after oral administration of metronidazole as compared with the intravaginal administration (71.1% vs 57.7%; P=0.023). The most common adverse events were nausea (30.4% with oral therapy vs 10.2% for vaginal therapy; P<0.001), abdominal pain (31.9% with oral therapy vs 16.8% for vaginal therapy; P=0.005), and headache (24.1% with oral therapy vs 31.1% for vaginal therapy; P=0.047). Nausea, abdominal pain and metallic taste as adverse events occurred significantly less often in patients treated with intravaginal metronidazole as compared to the orally treated patients.
Fischbach et al.[82] (1992) Metronidazole 500 mg BID for 7 days vs clindamycin phosphate vaginal cream 2% once daily for 7 days	RCT, DB, AC, MC Women ≥18 years of age diagnosed with bacterial vaginosis	N=407 39 days	Primary: Cure rate, post-treatment vulvovaginal candidiasis	Primary: There was no significant difference in cure rate for oral metronidazole (78%) and clindamycin vaginal cream (83%). The incidence of drug-related adverse effects was similar in both groups, approximately 12%. There was no significant difference in the rates of post-treatment vulvovaginal candidiasis associated with oral metronidazole (4.7%), and clindamycin vaginal cream (8.5%).
Arredondo et al.[83] (1992) Metronidazole 500 mg capsules BID for 7 days vs clindamycin vaginal cream 2% BID for 7 days	RCT, DB, MC Women with symptomatic bacterial vaginosis	N=184 50 days	Primary: Total healing rate, relapse rate, failure rate, adverse events	Primary: Improvement in total healing was 87% for clindamycin and 79% for metronidazole (P>0.22). While 7% of patients randomized to the metronidazole group developed relapse of the disease following treatment, none of the patients receiving topical clindamycin experienced a relapse. While clindamycin had a failure rate of 3%, 15% of patients in the metronidazole group failed treatment. Both drugs were well tolerated, with the most serious side effect, generalized rash, reported by a patient on metronidazole therapy.
Andres et al.[84]	RCT, DB, PC,	N=60	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1992) Metronidazole 500 mg capsules BID for 7 days vs clindamycin vaginal cream 2% BID for 7 days	PRO Non-pregnant women 18 to ≤60 years of age diagnosed with bacterial vaginosis	30 days	Cure rate, improvement rate, clinical failure assessed at the 1-week and 4-week follow-up visits, adverse events	There was no statistically significant difference between the metronidazole (82%) and clindamycin (97%) study groups at the 1-week follow-up visit in terms of patients who have either improved or were cured post-treatment. There was no statistically significant difference between the metronidazole (94.1%) and clindamycin (89.5%) study groups at the 4-week follow-up visit in terms of patients who had either improved or were cured post-treatment. There was no statistically significant difference in terms of clinical failure rate among patients randomized to receive either of the two study drugs. There was no statistically significant difference in side effects among patients randomized to receive either of the two study drugs.
Schmitt et al.[85] (1993) Metronidazole 500 mg capsules BID for 7 days vs clindamycin vaginal cream 2% QD for 7 days	RCT, DB, PC Nonpregnant women 18 to ≤60 years of age diagnosed with bacterial vaginosis	N=61 30 days	Primary: Overall healing rate (clinical and microbiological), symptomatic failure rate at the 1-week and 4-week follow-up visits, adverse events, *Candida* infections	Primary: There was no statistically significant difference in the overall cure rate between the metronidazole (87%) and clindamycin (72%) study groups at the 1-week follow-up visit (P=0.32). One month later, 61% of patients in both groups remained cured. Symptomatic failure occurred in one patient receiving clindamycin and in no one on metronidazole therapy. There were fewer asymptomatic failures in the metronidazole group compared to the clindamycin treatment arm; however this difference was not statistically significant (P=0.16). Symptomatic *Candida* yeast infections developed in 12% of clindamycin-treated patients and 9% of patients on metronidazole therapy. There was no statistically significant difference in side effects among patients randomized to receive either of the two study drugs.
Ferris et al.[86] (1993) Metronidazole 500	RCT, DB, AC Women ≥18 years of age diagnosed	N=101 14 days	Primary: Cure rate, post-treatment vulvovaginal	Primary: There was no significant difference in cure rates for oral metronidazole (84.2%), metronidazole vaginal cream (75%), or clindamycin vaginal cream (86.2%; P=0.548).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID for 7 days vs metronidazole vaginal gel BID for 5 days vs clindamycin vaginal cream 2% QD for 7 days	with bacterial vaginosis		candidiasis	There was no significant difference in the rates of post-treatment vulvovaginal candidiasis associated with oral metronidazole (12.5%), metronidazole vaginal cream (30.4%), or clindamycin vaginal cream (14.8%; P=0.272).
Higuera et al.[87] (2002) Metronidazole 500 mg capsules BID for 7 days vs clindamycin vaginal cream 2% QD for 7 days	RCT, DB, PC Women 16 to ≤60 years of age diagnosed with bacterial vaginosis	N=82 50 days	Primary: Cure rate, improvement, clinical failure rate, relapse rate Secondary: microbiological cure rate, vaginal fluid description, patient's efficacy evaluation, adverse effects	Primary: There was no statistically significant difference between the metronidazole (82%) and clindamycin (86%) study groups at the 1-week follow-up visit in terms of patients who have either improved or were cured post-treatment. There was no statistically significant difference in cure rate between the metronidazole (88%) and the clindamycin (90%) groups at the 4-week follow-up visit. There was no statistically significant difference in failure rate between the metronidazole (17.9%) and clindamycin (14.3%) treatment groups at the 1-week and 4-week follow-up visits. Secondary: There was no statistically significant difference in microbiological cure rate between the metronidazole (82%) and the clindamycin (86%) groups at the first follow-up visit. There was no statistically significant difference in patient self-reported cure rate between the metronidazole (82%) and clindamycin (86%) groups. There was a higher percentage of patients in the clindamycin group (10%)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				with a gram stain compatible with bacterial vaginosis at the second follow-up visit compared with the metronidazole group (4%; P<0.04). At the second follow-up visit, there were a greater number of patients in the clindamycin group (14%) exhibiting vaginal fluid odor compared to the metronidazole group (4%). There was no significant difference in the incidence of side effects between the metronidazole group (22%) and clindamycin (15%) group.
Paavonen et al.[90] (2005) Metronidazole 500 mg capsules BID for 7 days vs clindamycin 100 mg ovules administered intravaginally for 3 consecutive days	RCT, DB, AC, MC Women diagnosed with bacterial vaginosis	N=399 52 days	Primary: Overall clinical outcome, reported as cure, failure, and non-assessable efficacy rate Secondary: Clinical status, symptoms of vaginitis or cervicitis at each follow-up visit, patient evaluation of efficacy at second follow-up visit, adverse effects	Primary: No statistically significant difference between the two treatment groups was observed regarding the primary endpoint (95% CI, –10.6-13.4; P=0.810). There was no statistically significant difference in clinical status, at either the first or second follow-up visit, between the two treatment groups (P>0.5). There was no significant difference in the proportion of patients in the metronidazole treatment group who rated their vaginal infection as cured (79.6%) vs the proportion of patients randomized to clindamycin therapy who considered themselves cured (78.3%). There was no difference in the number of patients reporting symptoms of vaginitis and cervicitis at either the first or second follow-up visit. Treatment-related adverse effects were more frequent in the metronidazole group (16.3%), compared to the clindamycin treatment group (10.3%), but this difference was not statistically significant (P=0.104).
Mohanty et al.[67] (1987) Metronidazole 2 g single dose vs	RCT Women with bacterial vaginosis associated with *Gardnerella vaginalis*	N=280 6 weeks	Primary: Cure (defined as negative culture for *G vaginalis* and absence of 3 or more of 4 criteria), recurrence (positive result	Primary: Cure was achieved in 79.4%, 88.0% and 92.3% of patients receiving metronidazole, nimorazole and tinidazole, respectively. There were no significant differences between the treatment groups. The overall recurrence rate was 21% with metronidazole, 26% with nimorazole and 14% with tinidazole and was believed to be due to reinfection from the untreated partners rather than to relapse.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tinidazole 2 g single dose vs nimorazole* 2 g single dose			after 2 weeks), adverse events	Mild adverse effects were reported in 46.3% of patients receiving metronidazole, 28.0% of patients receiving nimorazole and 32.7% of patients receiving tinidazole.
Schwebke et al.[96] (2011) Metronidazole 500 mg BID for 7days vs tinidazole 500 mg BID for 7 days vs tinidazole 1 g BID for 7 days	PRO, RCT, OL Women with bacterial vaginitis with no evidence of STDs	N=593 28 days	Primary: Microbiologic cure Secondary: Clinical improvement; cure; clinical failure	Primary: At the 14-day follow-up, failures (Nugent score ≥7) were not different between the metronidazole group (17.7%), the tinidazole 1 g group (27%) or the tinidazole 500 mg group (24.7%; P=0.16). At the 14-day follow-up, there was no difference in the microbiologic cure (Nugent score <7) in the metronidazole group (82.4%), the tinidazole 1 g group (73%), or the tinidazole 500 mg group (75.3%; P=0.08). At the 28-day follow-up, the microbiologic cure or improvement rate (Nugent score <7) was not different between the metronidazole group (55.2%), the tinidazole 1 g group (62.3%), or the tinidazole 500 mg group (58%; P=0.08). There was no difference in recurrence rates between the treatment groups at the 1- or 2-month follow-up visits. There were no differences in adverse events between groups, except for a higher incidence of taste perversion (41.8%) in the tinidazole 1 g group compared to metronidazole (11%) and tinidazole 500 mg (15.2%; P<0.001).
Ekgren et al.[68] (1988) Tinidazole 2 g for 1 or 2 days vs placebo	DB, PC, RCT Women with nonspecific bacterial vaginosis	N=247 2 weeks	Primary: Cure (defined as absence of both clue cells and *G vaginalis)*	Primary: Cure rates were 74% for the 2-day regimen and 51% for the single-dose regimen and 4% for placebo (P<0.001 vs placebo for both active treatments, P<0.02 tinidazole 2-day regimen versus single-dose regimen).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Carmona et al.[69] (1983) Tinidazole 2 g as a single dose	OL Women with bacteriologic and clinical diagnosis of *G vaginalis* vaginitis	N=30 30 days	Primary: Bacteriologic cure, clinical cure	Primary: Bacteriologic and clinical cure rates after 1 week were 90% and 93%, respectively.
Livengood et al.[79] (2007) Tinidazole 1 g once daily for 5 days or tinidazole 2 g once daily for 2 days vs placebo	RCT, DB, PC Women ≥18 years of age with bacterial vaginosis	N=235 10 days	Primary: Cure rates Secondary: Adverse events	Primary: Treatment with tinidazole 1 g once daily for 5 days resulted in a cure rate of 36.8% (P<0.001; number needed to treat 3.2) and a cure rate of 27.4% with tinidazole 2 g once daily for 2 days (P<0.001; number needed to treat 4.5) as compared to placebo (5.1% cured). Secondary: Adverse events occurred with comparable frequency in tinidazole and placebo recipients, except for dysgeusia, which was significantly more common in the tinidazole arms. However, no difference was seen between the tinidazole and placebo groups in the number of participants experiencing one or more gastrointestinal symptoms.
Cryptosporidiosis				
Rossignol et al.[41] (2001) Nitazoxanide 500 mg BID (12-65 years), 200 mg BID (4-11 years) or 100 mg BID (1-3 years) for 3 days vs placebo	DB, PC, RCT Immunocompetent adults and children with diarrhea and *Cryptosporidium parvum* oocysts in stool (Egypt)	N=98 7-10 days	Primary: Clinical response at day 7, parasitological response 7-10 days after treatment initiation Secondary: Time to passage of last unformed stool, adverse events	Primary: At 7 days after initiation of therapy, diarrhea had resolved in 39 (80%) of the 49 patients in the nitazoxanide treatment group, compared with 20 (41%) of 49 in the placebo group (P<0.0001). Parasitological response (no oocysts in either of the 2 posttreatment stool samples) was reported in 33 (67%) of patients in the nitazoxanide group compared with 11 (22%) in the placebo group (P<0.0001). Nitazoxanide treatment reduced the duration of both diarrhea (P<0.0001) and oocyst shedding (P<0.0001). Secondary: Diarrhea was resolved in most patients receiving nitazoxanide within 3 or 4 days of treatment initiation. In the placebo group, 59% of patients still had diarrhea at the end of the follow-up period. Safety and tolerance data were similar among the nitazoxanide and placebo treatment groups, with no serious adverse event occurring.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Therapy was discontinued due to dizziness in 1 patient receiving nitazoxanide and 1 patient receiving placebo.
Rossignol et al.[42] (2006) Nitazoxanide 500 mg tablets BID for 3 days vs nitazoxanide 500 mg suspension BID for 3 days vs placebo	DB, PC, RCT Immunocompetent patients 12 years and older with *Cryptosporidium* as the sole cause of diarrhea (Egypt)	N=86 7-10 days	Primary: Clinical response at day 7 Secondary: Microbiologic response at day 7-10 after treatment initiation	Primary: The proportion of patients reporting a well response (no symptoms, no watery stools and no more than 2 soft stools, and no hematochezia within the past 24 hours or no symptoms and no unformed stools within the past 48 hours) was 96%, 87% and 41% for the nitazoxanide tablets (P<0.0001), nitazoxanide suspension (P=0.0003) and placebo, respectively. Secondary: The proportion of patients with no *Cryptosporidium* oocysts detected in posttreatment stool samples was 93% (P<0.0001), 90% (P<0.0001) and 37% for nitazoxanide tablets, nitazoxanide suspension and placebo, respectively.
Amadi et al.[43] (2002) Nitazoxanide 100 mg BID for 3 days vs placebo	PC, RCT Zambian children >1 year old with diarrhea due to *C parvum*, stratified by HIV serology	N=100 10 days	Primary: Clinical response on day 7 after start of treatment Secondary: Parasitological response by day 10, mortality by day 8, adverse events	Primary: In HIV-negative children, diarrhea resolved in 56% and 23% of patients receiving nitazoxanide and placebo, respectively (difference 33%, 95% CI: 7 to 59; P=0.037). In HIV-positive children, diarrhea resolved in 8% and 25% of patients receiving nitazoxanide and placebo, respectively (difference –17%, 95% CI: –37 to 3; P=0.14). Secondary: *C parvum* was eradicated from stool in 52% and 14% of HIV-negative children receiving nitazoxanide and placebo, respectively (38%, 95% CI: 14 to 63; P=0.007). There was no difference in parasitological response in HIV-positive children receiving nitazoxanide (16%) or placebo (21%) (P=1.0). None of the HIV-negative children in the nitazoxanide group died compared to 18% of children in the placebo group (–8%, 95% CI: –34% to 2; P=0.041). There was no difference in mortality rate among HIV-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				positive children receiving nitazoxanide (20%) or placebo (17%) (P=1.0). Nitazoxanide was not significantly associated with adverse events in either stratum.
Rossignol et al.[44] (1998) <u>Group 1</u> Nitazoxanide 500 mg plus placebo BID for 14 days, then placebo for 14 days vs <u>Group 2</u> nitazoxanide 1,000 mg BID for 14 days, then placebo for 14 days vs <u>Group 3</u> placebo for 14 days, then randomized to one of the above nitazoxanide regimens for 14 days	DB, PC, RCT Adult HIV-positive patients aged 18-65 years with *C parvum* diarrhea (Mexico)	N=54 7-10 days	Primary: Parasitological cure (no *C parvum* oocysts observed in 3 consecutive stool samples at 7-day intervals, starting on day 15 of the trial), clinical cure (assessed on days 15 and 29 and defined as diarrhea completely resolved and no longer suffered from accompanying symptoms)	Primary: Parasitological cure was reported in 12 patients in Group 1 (63%; P=0.016 vs placebo) and 10 patients in Group 2 (67%; P=0.013 vs placebo) but only in 5 patients (25%) receiving placebo (Group 3). There was a correlation between parasitological cure and patient CD4 count. Pooled data taken from the 10 patients with a CD4 count <50 cells/mm^3 showed that only 30% achieved parasitological cure, which was not significantly different than patients receiving placebo (40%). In patients with a CD4 count >50 cells/mm^3, nitazoxanide yielded a 79% (N=19) parasitological cure rate as opposed to 20% (N=3) for patients receiving placebo. Thus, the lower the CD4 count of patients, the less likely they are to respond to nitazoxanide therapy. Upon follow-up on days 15 and 29, 92% and 80% of patients achieving parasitological cure also demonstrated clinical cure in Groups 1 and 2, respectively. There were a total of 53 adverse reactions reported in the study, none of which were labeled as related or probably related to treatment with nitazoxanide. There were, however, 16 adverse reactions that were categorized as possibly related to nitazoxanide therapy, the most common being vomiting (10), anemia (4), jaundice (1), and hematuria (1).
Rossignol et al.[45] (2006) Nitazoxanide 500-1,500 mg BID in adults and 8 mg/kg–23 mg/kg BID in	MC, OL Patients ≥3 years of age who were HIV-positive and had at least 2 weeks of diarrhea	N=357 1 day-4 years	Primary: Clinical response (changes in global assessment of symptoms and global assessment of overall health	Primary: Among the 357 patients included in the intent-to-treat analysis, 209 (59%) achieved a sustained clinical response while on treatment. Mean time to clinical response was 2 weeks. Among the 202 patients who submitted at least one stool sample, 116 patients (57% of evaluable patients) had *Cryptosporidium*-negative stool at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
children	(4 weeks if CD4 count >200/mm3) and positive stool for *C parvum* oocysts		over time) and parasitological response at weeks 1, 2, 4, and monthly thereafter while patients was on treatment, adverse events	the last examination before completing the study while 86 (43%) patients had *Cryptosporidium*-positive stool. The mean time to first negative stool examination was 7 weeks. Clinical responses were closely associated with Cryptosporidium-negative stools (P<0.0001). Among the evaluable patients, relationships between CD4 count and last parasitology result were apparent (P=0.072 and P=0.0051, respectively), and those with higher CD4 counts were more likely to achieve both the sustained clinical response and negative parasitology results. Twenty-seven nonserious adverse events were considered possibly related to the use of the study drug. Most of these events were associated with the digestive tract (nausea, vomiting, diarrhea, abdominal pain and dyspepsia). No safety issues were identified at doses up to 3,000 mg/day or for long durations of treatment. Nitazoxanide can be considered useful therapy for treatment of patients with AIDS-related cryptosporidiosis.
Abubakar et al.[77] (2007) Nitazoxanide or paromomycin	MA Immuno-compromised individuals with cryptosporidiosis	N=169 Variable duration	Primary: Durations of diarrhea, mortality, parasitological clearance Secondary: Adverse events	Primary <u>Nitazoxanide (2 studies)</u> Two studies showed no evidence that nitazoxanide is more effective in reducing the frequency of diarrhea than placebo (RR 0.83; 95% CI, 0.36-1.94). One study reported data on deaths which showed a RR of 0.61 (95% CI, 0.22-1.63) among all 96 children based on five and eight deaths in the intervention and control arms, respectively. Treatment with nitazoxanide led to a significant parasitological response compared with placebo among all children with a RR of 0.52 (95% CI, 0.30-0.91). The effect was not significant for HIV-seropositive participants (RR 0.71; 95% CI, 0.36-1.37). HIV-seronegative participants on nitazoxanide had a significantly higher RR of achieving parasitological clearance of 0.26 (95% CI, 0.09-0.80) based on a single study.

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				Paromomycin (2 studies) Two studies showed no evidence that paromomycin is more effective in reducing the frequency of diarrhea than placebo (RR 0.74; 95% CI, 0.42-1.31). The use of paromomycin did not significantly lead to a parasitological response (RR 0.73; 95% CI, 0.38-1.39). Secondary: Adverse events occurred infrequently in all studies.
Giardiasis				
Ortiz et al.[47] (2001) Metronidazole 125 mg BID (5-6 years of age) or 250 mg BID (6-11 years of age) for 5 days vs nitazoxanide 100 mg BID (2-3 years of age) or 200 mg BID (4-11 years of age) for 3 days	RCT Children aged 2-11 years with acute or chronic diarrhea and cysts of *G intestinalis* in a stool sample 7 days prior to the start of the study (Peru)	N=110 7-10 days	Primary: Clinical response at day 7 follow-up visit Secondary: Parasitological response at 7-10 days, adverse events	Primary: Diarrhea had resolved in 80% and 85% of the children treated with metronidazole and nitazoxanide, respectively, before day 7 follow-up visit (P=0.6148). Diarrhea resolved within 4 days in 75% and 87% of children treated with metronidazole and nitazoxanide, respectively. Secondary: The proportions of children with no cysts of *G intestinalis* collected 7-10 days following metronidazole and nitazoxanide were 75% and 71%, respectively (P=0.8307). Fourteen children, 7 in the metronidazole group and 7 in the nitazoxanide group reported that they had missed one or more doses of study medication (range 1-9 doses, mean 4.57 for metronidazole; range 1-5 doses, mean 3 for nitazoxanide). Only mild, transient adverse events were reported.
Gazder et al.[48] (1978) Metronidazole 50 mg/kg as a single dose	OL, PG, RCT Children mean age 5.5 years with symptoms of giardiasis and stools positive for	N=100 16 days	Primary: Clinical success (relief of all symptoms and stools negative for *Giardia*), adverse events	Primary: Symptom relief and parasitic clearance were obtained in 36.0% (18/50) of patients receiving metronidazole and 80.0% (40/50) of patients treated with tinidazole (P<0.01). Adverse events, including mild nausea, vomiting and bitter taste were reported in 4.0% of patients receiving metronidazole and 12.0% of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tinidazole 50 mg/kg as a single dose	cysts or trophozoites of *G duodenalis* (India)			receiving tinidazole.
Bakshi et al.[30] (1978) Metronidazole 50 mg/kg as a single dose vs tinidazole 50 mg/kg as a single dose	PG, RCT Children mean age 5.8 years with abdominal symptoms and *Giardia* cysts in stool (India)	N=186 16 days	Primary: Clinical success (relief of all symptoms and stools negative for *Giardia*), adverse events	Primary: Clinical success was achieved in 46.7% (43/92) of patients given metronidazole versus 88.3% (83/94) of patients given tinidazole (P<0.01). Mild gastrointestinal adverse events were reported in 2.2% and 8.8% of patients receiving metronidazole and tinidazole.
Krishnamurthy et al.[49] (1978) Metronidazole 50 mg/kg as a single dose vs tinidazole 50 mg/kg as a single dose	PG, RCT Pediatric patients with symptomatic giardiasis	N=60 12 days	Primary: Cure	Primary: Cure was reported in 50.0% and 96.7% of patients receiving metronidazole and tinidazole, respectively (P<0.01).
Nigam et al.[50] (1991) Metronidazole 50 mg/kg as a single dose vs tinidazole 50 mg/kg	PG, RCT Young adults with giardiasis (India)	N=75 12 days	Primary: Cure (negative stools and symptoms), adverse effects	Primary: Cure was reported in 54.3% and 97.5% of patients receiving metronidazole and tinidazole, respectively (P<0.01). Overall adverse events were reported in 5.7% and 12.5% of patients receiving metronidazole and tinidazole, respectively. The most frequently reported adverse events were gastrointestinal discomfort, nausea, vomiting, and bitter metallic taste.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
as a single dose				
Jokipii et al.[51] (1979) Metronidazole 2.4 g as a single dose vs metronidazole 2.4 g per day for 2 days vs tinidazole 2 g as a single dose	OL, PG Adults with symptoms of giardiasis and stools positive for cysts or trophozoites of *G duodenalis* (Finland)	N=85 8 weeks	Primary: Cure rates (clinical assessment and stool samples at 1, 2, 4, and 8 weeks after completion of treatment), adverse events	Primary: Cure rates were 50.0% in those who received metronidazole single dose, 77.4% in those who received metronidazole multiple dose and 92.9% in patients who received tinidazole single dose (P<0.001 metronidazole single dose vs tinidazole single dose; P=NS metronidazole multiple dose vs tinidazole single dose, P<0.05 metronidazole multiple dose vs single dose). Adverse effects were mild across groups and included metallic taste, nausea and fatigue occurring in 92.3% metronidazole single dose, and 90.3% metronidazole multiple dose, and 75.0% tinidazole single dose.
Kyronseppa et al.[52] (1981) Metronidazole 2 g per day for 2 days vs tinidazole 2 g as a single dose	PG, RCT Adults with symptoms of giardiasis and stools positive for *Giardia* (Finland)	N=50 4 weeks	Primary: Cure (disappearance of symptoms), adverse events	Primary: Cure was reported in 76.0% and 88.0% of patients receiving metronidazole and tinidazole, respectively (P=NS). A 1-week course of metronidazole (200 mg TID) was successful in 8/9 failures. Overall adverse events were reported in 28.0% of patients receiving metronidazole and 17.9% of patients receiving tinidazole with nausea, fatigue, drowsiness and GI discomfort (metronidazole) most frequently reported.
Speelman et al.[53] (1985) Study 1 Metronidazole 60 mg/kg single dose up to 2.4 g vs	RCT Infants through adults infected with *Giardia lamblia* (Bangladesh)	Study 1 N=33 4 weeks Study 2 N=30 4 weeks	Primary: Parasitological cure (no *G lamblia* cysts or tropho-zoites in fecal specimens), adverse events (only Study 2)	Primary: After 4 weeks, the eradication rates following single doses of metronidazole and tinidazole in Study 1 were 56% (9/16) and 94% (16/17), respectively (P<0.02). In Study 2, eradication rates were 93.3% (14/15) with metronidazole 3-day regimen versus 100% (15/15) with tinidazole single dose. No serious side effects were encountered in either group. There were no statistically significant differences in side effects reported in patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tinidazole 50 mg/kg single dose up to 2 g Study 2 Metronidazole 50 mg/kg single dose up to 2 g for 3 days vs tinidazole 50 mg/kg single dose up to 2 g				receiving tinidazole single dose versus the metronidazole 3-day regimen. Problems with the administration of the syrup to children, because of an unpleasant taste, were only reported in the tinidazole group (P<0.05).
Suntornpoch et al.[54] (1981) Metronidazole 20 mg/kg for 5 days vs ornidazole* 50 mg/kg single dose (maximum 2 g) vs tinidazole 50 mg/kg single dose (maximum 2 g)	RCT Children with *G lamblia* (cysts or trophozoites) in stool specimens (Thailand)	N=121 21 days	Primary: Cure (negative stools and relief of symptoms)	Primary: Cure was reported in 32/33 patients receiving metronidazole, 38/40 ornidazole and 45/48 of tinidazole (P>0.05).
Rossignol et al.[46] (2001) Nitazoxanide 500 mg BID for 3 days vs	DB, PC, RCT Patients aged 12-65 years with diarrhea caused by *Giardia intestinalis* and/or *Entamoeba histolytica* and/or *E*	N=89 7-10 days	Primary: Clinical response at day 7, parasitological response (no cysts observed in 2 posttreatment stool examinations) at 7-	Primary: After initiation of treatment, diarrhea resolved within 7 days in 81% of patients in the nitazoxanide group versus 40% in the placebo group (P=0.0002). The parasitological response rate for *G intestinalis* was 71% for the nitazoxanide group versus 0% for the placebo group (P<0.0001). For *E histolytica* and/or *E dispar*, the parasitological response rate for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	*dispar* (Egypt)		10 days Secondary: Date of last unformed stool, adverse events	nitazoxanide group was 69% versus 39% for the placebo group (P=0.0148). Secondary: The median time from initiation of therapy to passage of the last unformed stool was 3 days in the nitazoxanide group, but could not be calculated in the placebo group since 60% of the patients still had diarrhea at the end of the follow-up period. All of the adverse events were mild and transient in nature, with none resulting in discontinuation of therapy.
Escobedo et al.[76] (2008) Nitazoxanide 7.5 mg/kg twice daily for 3 days (NTZ) vs tinidazole 50 mg/kg as a single dose (TIN)	RCT, OL Children 5-15 years of age infected with *G. lamblia* with or without diarrhea	N=166 7 days following treatment	Primary: Response to treatment and adverse events	Primary: The frequency of parasitological cure seen in children given TIN was significantly higher than that obtained with NTZ (90.5% vs 78.4%; P<0.05). Diarrhea stopped within 6 days of completing treatment in all 33 children in the NTZ group who had diarrhea at enrollment and in 19 of the 20 children in the TIN group who had diarrhea at enrollment. The median times taken for diarrhea to resolve were 4 days after completing NTZ treatment and 3 days after completing TIN treatment. Both treatments were well tolerated. Adverse events occurred in 43.2% of patients in the NTZ group and in 22.2% of patients in the TIN group. All adverse events were graded as mild and transient and did not require medication or discontinuation of treatment. Apart from a bitter taste (reported by 17.5% of the children given TIN and none of those given NTZ; P<0.05) and unusually yellowish urine (reported by 36.5% of the children given NTZ and none of those given TIN; P<0.05), there were no significant differences in the incidences of any of the adverse events among the treatment groups.
Prevention of *Pneumocystis* Pneumonia (PCP)				
El-Sadr et al.[57] (1998) Atovaquone 1,500 mg QD	RCT, MC, OL Patients ≥13 years old with a history of PCP, or with a	N=1,057 Mean 27 months	Primary: Onset of probable or micro-biologically confirmed PCP	Primary: There was no statistically significant difference in PCP development between the dapsone- and atovaquone-treated groups (RR 0.85; 95% CI: 0.67 to 1.09; P=0.20).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs dapsone 100 mg QD	CD4 cell count no higher than 200 per mm^3 or no more than 15% of the total lymphocyte count, and a history of treatment-limiting reaction to sulfonamides or trimethoprim		Secondary: Confirmed or probable toxoplasmosis, death, combined end point of death or PCP, discontinuation of the drug due to intolerable adverse events	Secondary: There was no statistically significant difference in toxoplasmosis development between the dapsone- and atovaquone-treated groups (RR=1.18; 95% CI: 0.26 to 5.30; P=0.83). There was no statistically significant difference in mortality between the dapsone- and atovaquone-treated groups (RR=1.07; 95% CI: 0.89 to 1.30; P=0.45). There was no statistically significant difference in the cumulative endpoint between the two groups (RR=0.98; 95% CI: 0.89 to 1.16; P=0.80). There was no statistically significant difference in the number of patients discontinuing treatment because of intolerable toxicity between the two groups (RR=0.94; 95% CI: 0.74 to 1.19; P=0.59). Among patients receiving a dapsone-based prophylactic regimen at baseline, the risk of discontinuation due to adverse effects was higher in the atovaquone group (RR=3.78; 95% CI: 2.37 to 6.01; P<0.001). Among patients not receiving a dapsone-based prophylactic regimen at baseline, the risk of discontinuation due to adverse effects was lower in the atovaquone group (RR=0.42; 95% CI: 0.30 to 0.58; P<0.001). Among patients who cannot tolerate SMX-TMP, atovaquone and dapsone are similarly effective for the prevention of PCP. Our results support the continuation of dapsone prophylaxis among patients who are already receiving it. However, among those not receiving dapsone, atovaquone is better tolerated and may be the preferred choice for prophylaxis against PCP.
Chan et al.[59] (1999) Atovaquone 750 mg or 1,500 mg once daily	OL, PG, RCT Patients with HIV who met standard criteria for PCP prophylaxis, were intolerant to	N=549 Median time using assigned therapy was 6.6 months and median	Primary: Incidence of PCP Secondary: Mortality, combined end point of PCP or	Primary: There was no significant difference in the incidence of PCP in patients receiving atovaquone 750 mg, atovaquone 1,500 mg or aerosolized pentamidine (25%, 22%, and 17%, respectively). Compared to aerosolized pentamidine, the RR were 1.41 (95% CI: 0.90 to 2.22) and 1.26 (95% CI: 0.78 to 2.03) for atovaquone 750 mg and 1,500 mg, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pentamidine aerosolized 300 mg once a month	sulfonamides and/or trimethoprim, did not have evidence of active PCP, were at least 13 years of age, and did not have marked abnormalities in laboratory tests of hematologic, renal, hepatic and pancreatic function	follow-up was 11.3 months	death, incidence of adverse events	Secondary: There were no statistically significant differences among subjects with regard to mortality (22%, 15% and 19%, respectively). Compared to aerosolized pentamidine, the RR was 1.12 (95% CI: 0.72 to 1.75) and 0.75 (95% CI: 0.46 to 1.24) for atovaquone 750 mg and 1,500 mg, respectively. The combined occurrence of PCP or death was not significantly different among the subjects (37%, 30% and 30%, respectively). The incidence of adverse events was significantly higher with atovaquone than aerosolized pentamidine (P<0.01). The most frequent adverse events in both atovaquone groups were rash, diarrhea, vomiting, and nausea. In the aerosolized pentamidine group, respiratory events (bronchospasm, cough, and dyspnea) were the most frequent adverse events.
Hughes et al.[58] (1993) Atovaquone 750 mg TID for 21 days vs SMX-TMP 1,600-320 mg TID for 21 days	DB Patients with AIDS and mild (alveolar-arterial oxygen gradient <35 mm Hg) or moderately severe (alveolar-arterial oxygen gradient 35-45 mm Hg) PCP	N=322 8 weeks	Primary: Therapeutic failure due to lack of efficacy, treatment-limiting adverse effects (TLAEs), successful therapy, survival	Primary: SMX-TMP was more effective than atovaquone in treating PCP with 7% and 20%, respectively, of patients considered to have therapeutic failure measured one month after therapy (P=0.0002). TLAEs requiring a change in therapy occurred more frequently in patients receiving SMX-TMP (20%) than atovaquone (7%) (P=0.001). Significantly higher rates (P<0.05) were reported in the SMX-TMP group than in the atovaquone group for nausea (44% vs 20%), vomiting (35% vs 14%), constipation (17% vs 3%), dizziness (8% vs 3%), fever (25% vs 14%) and rash (34% vs 23%). Diarrhea occurred more frequently during treatment with atovaquone (19%) than SMX-TMP (7%) (P<0.05), but it was not associated with lack of efficacy or treatment-limiting adverse effects. Within 4 weeks of the completion of treatment, there were 11 deaths in the atovaquone group (4 due to PCP) and 1 death in the SMX-TMP group (due to AIDS wasting syndrome) (P=0.003). Diarrhea at entry was associated with lower plasma drug concentrations (P=0.009), therapeutic failure (P<0.001), and death (P<0.001) in the atovaquone group but not in the SMX-TMP group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Atovaquone was less effective than SMX-TMP, but had fewer treatment-limiting adverse effects.
Ioannidis et al.[61] (1996) Pentamidine, aerosolized vs dapsone-based regimens vs SMX-TMP vs placebo	MA Trials comparing dapsone, aerosolized pentamidine, or SMX-TMP in preventing PCP	N=6,583 (35 trials) Variable duration	Primary: Number of *P jiroveci* episodes, *P jiroveci*-related deaths, toxoplasmosis episodes, all-cause mortality	Primary: There was a significant decrease in the incidence of *P jiroveci* events in patients on any primary or secondary prophylactic regimen compared to placebo (RR 0.39; 95% CI, 0.27-0.55 and RR 0.16; 95% CI, 0.08-0.35, respectively). There was no significant difference in mortality between the different prophylactic regimens in all 35 trials. Oral prophylactic regimens were significantly more effective in reducing *P jiroveci* events compared to aerosolized pentamidine (RR=0.39; 95% CI, 0.27-0.55). Oral prophylactic regimens were significantly more effective in reducing toxoplasmosis events compared to aerosolized pentamidine (RR=0.67; 95% CI, 0.50-0.88). There was no statistically significant difference in the occurrence of *P jiroveci* and toxoplasmosis events between patients receiving SMX-TMP or dapsone-based regimens (RR=0.61; 95% CI, 0.34-1.10 and RR 1.26; 95% CI, 0.68-2.34, respectively). While SMX-TMP exhibited greater efficacy in reducing *P jiroveci* events (RR=0.58; 95% CI, 0.45-0.75), dapsone-based regimens were comparable to the aerosolized pentamidine regimen (RR=0.93; 95% CI, 0.72-1.19). Compared with aerosolized pentamidine, oral regimens were overall 5 times more likely to be discontinued due to adverse events (RR=5.38; 95% CI, 3.69-7.83). There was no significant difference between the SMX-TMP and dapsone-based regimens in the patient attrition rate as a result of treatment-related adverse effects (RR=1.30; 95% CI, 1.04-1.62). SMX-TMP-treated groups exhibited the smallest prophylaxis failure rates,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				0.5% for both primary and secondary prophylaxis.
Bucher et al.[62] (1997) Pentamidine, aerosolized vs dapsone vs dapsone-pyrimethamine vs SMX-TMP	MA Trials comparing dapsone, dapsone-pyrimethamine, aerosolized pentamidine or SMX-TMP in preventing PCP events	N=4,870 (22 trials) Variable duration	Primary: Opportunistic infections with PCP, *Toxoplasma* encephalitis, or both, mortality, drug-limiting toxicity requiring a change in therapy	Primary: Compared to aerosolized pentamidine, dapsone-based regimens were more effective in preventing PCP events (RR 0.90; 95% CI: 0.71 to 1.15) but not significantly different in terms of *Toxoplasma* encephalitis prevention (RR 0.78; 95% CI: 0.55 to 1.11). Compared to dapsone-based regimens, SMX-TMP was more effective in preventing PCP events (RR 0.49; 95% CI: 0.26 to 0.92) but not significantly different in terms of *Toxoplasma* encephalitis prevention (RR 1.17; 95% CI: 0.68 to 2.04). SMX-TMP was significantly more effective compared to aerosolized pentamidine in preventing PCP events (RR 0.59; 95% CI: 0.45 to 0.76). Drug-limiting toxicity was experienced by 29.7% of patients treated with a dapsone-based regimen, 6.8% of patients treated with aerosolized pentamidine, and 31.5% of patients on SMX-TMP therapy. There was no significant difference in mortality between the dapsone-based regimen and SMX-TMP (RR 0.98; 95% CI: 0.80 to 1.08, P>0.20) or the aerosolized pentamidine regimen (RR 1.07; 95% CI: 0.90 to 1.27, P>0.18). The mortality risk ratio in patients with CD4 cell count <100 cells/mm^3 treated with SMX-TMP compared with dapsone-based regimen was 0.43 (95% CI: 0.21 to 0.88). Mortality was lower in the SMX-TMP-treated group compared with patients on the aerosolized pentamidine therapy (RR 0.88; 95% CI: 0.74 to 1.06, P=0.04).
Green et al.[88] (2007) Atovaquone vs	MA Immuno-compromised patients with cancer, bone	N=1,155 (11 trials) Variable duration	Primary: Documented Pneumocystis infections Secondary:	Primary: There was a significant reduction in the occurrence of PCP infections in the TMP/SMX 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pentamidine vs TMP/SMX dapsone vs pyrimethamine vs clindamycin vs mycophenolate mofetil	marrow transplant patients, solid organ transplant patients, patients receiving corticosteroids, patients receiving other immune suppressive medications, severe malnutrition, primary immune-deficiency diseases		All-cause mortality at end of study follow-up, PCP-related mortality at end of study follow-up, infections other than Pneumocystis	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 TMP/SMX prophylaxis versus a non anti-PCP antibiotic (quinolones). Prophylaxis with TMP/SMX was better than 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 TMP/SMX to placebo, RR 0.79 (95% CI 0.18 to 3.46), and two trials compared TMP/SMX versus quinolones, RR 0.49 (95% CI 0.02 to 10.73). TMP/SMX prophylaxis reduced PCP-related mortality, RR 0.17 (95% CI 0.03 to 0.94).Four trials compared TMP/SMX 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 TMP/SMX versus quinolones. PCP related mortality was reduced in the TMP/SMX group, RR 0.14 (95% CI 0.01 to 2.65). In the analysis of any infection other than PCP, 0ne study comparing TMP/SMX 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 TMP/SMX prophylaxis versus quinolones found significantly more infections other than PCP in the TMP/SMX arm compared to quinolones, RR 1.59 (95% CI 1.17 to 2.14).
Treatment of *Pneumocystis* Pneumonia (PCP)				
Dohn et al.[55] (1994) Atovaquone 750 mg PO with meals TID vs pentamidine IV 3-4 mg/kg once daily	OL, RCT Patients with HIV infection and clinical presentations consistent with mild or moderate PCP, 75% of patients were	N=109 8 weeks	Primary: Therapy success (sustained clinical improvement 4 weeks after therapy was discontinued), therapy failure because of absence of response or due to adverse events	Primary: Fifty-seven percent of patients treated with atovaquone and 40% of patients treated with pentamidine were clinically improved 4 weeks after therapy was discontinued (P=0.085). Twenty-nine percent of patients treated with atovaquone were considered treatment failures compared to 17% of patients treated with pentamidine (P=0.18). Discontinuation of treatment due to adverse events was more common

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	intolerant of sulfonamides or trimethoprim			with pentamidine (36%) than with atovaquone (4%; P<0.001). The most common treatment-limiting adverse events (TLAEs) for pentamidine were hypoglycemia (11%), vomiting (8%), nausea (7%), elevated creatinine level (6%) and rash (6%). Rash (4%) was the most common TLAE in patients receiving atovaquone. Nine patients in each treatment group died during the study (P=0.65), with death attributed to PCP in 4 patients receiving atovaquone and 3 patients receiving pentamidine.
Kim et al.[95] (2009) Pentamidine vs clindamycin-primaquine (C-P)	RETRO Korean patients with PCP	N=23 6 months	Primary: Treatment failure (inability to maintain a PaO2 despite increases in FiO2; deterioration of vital signs with a requirement for increased FiO2 after 7 days); positive response: (resolution of baseline signs and symptoms and CXR; decreased O2 requirements after therapy)	Primary: The response rate for patients treated with C-P was higher than that for pentamidine only (64% vs 11%, respectively; P=0.03). Response rates were higher in patients treated with C-P who had previously failed to respond to trimethoprim-sulfamethoxazole (43%) compared to pentamidine (11%; P=0.26). Patients with HIV had a response rate of 71% with C-P compared to 57% for those without HIV (P=1.00). Patients with HIV had a response rate of 0% with pentamidine compared to 20% for those without HIV (P=1.00).
Smego et al.[56] (2001) Pentamidine, atovaquone, trimetrexate, eflornithine, clindamycin-primaquine, SMX-TMP,	MA HIV-infected patients with confirmed PCP in whom initial anti-pneumocystis treatment failed and the patient required alternative drug therapy	N=497 Variable duration	Primary: Positive response to salvage therapy	Primary: Efficacies of salvage regimens were as follows: clindamycin-primaquine (88% to 92%), atovaquone (80%), eflornithine hydrochloride (57%; P<0.01), SMX-TMP (53%; P<0.08), pentamidine (39%), and trimetrexate (30%). The combination of clindamycin plus primaquine appears to be the most effective alternative treatment for patients with PCP who are unresponsive to conventional anti-pneumocystis agents.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Trichomoniasis				
O-Prasertsawat et al.[64] (1992) Metronidazole 1.6 g divided into 2 doses vs tinidazole 2 g single dose	DB, PG, RCT Women with vaginal trichomoniasis (Thailand)	N=132 Follow-up 6-16 days	Primary: Clinical cure, adverse effects	Primary: Microbiologic cure was reported in 98.5% and 100% of patients receiving metronidazole and tinidazole, respectively (P=NS). The most frequently reported adverse events were bitter taste: 36.9% with tinidazole vs 23.9% with metronidazole, and nausea and vomiting (20.0% vs 17.9%, respectively).
Gabriel et al.[65] (1982) Metronidazole 2 g as a single dose vs tinidazole 2 g as a single dose	PG, RCT, SB Women with vaginal trichomoniasis	N=82 2 weeks	Primary: Clinical cure (absence of *T vaginalis* on vaginal smears and negative cultures), adverse events	Primary: Clinical cure was reported in 97.5% and 95.3% of patients receiving metronidazole and tinidazole, respectively (P=NS). No adverse events were reported with either regimen.
Aimakhu et al.[66] (1975) Metronidazole 200 mg TID for 7 days vs tinidazole 2 g as a single dose	PG, RCT, SB Women with vaginal trichomoniasis	N=50 7 days	Primary: Microscopic cure	Primary: Microscopic cure was reported in 100% and 96.0% of patients receiving metronidazole and tinidazole, respectively (P=NS).
Forna et al.[63] (2003) Various antitrichomonal	MA Symptomatic or asymptomatic women, including	54 trials Duration varied	Primary: Parasitological cure, clinical cure (clearance of discharge,	Primary: Two trials compared different doses of short treatment metronidazole. Doses of metronidazole 1 g or less were less effective than doses of 1.5 g or more in terms of failure to achieve parasitological cure (RR 2.97, 95% CI: 1.92 to 4.59) with similar rates of side effects.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
regimens, including oral and vaginal products, single-dose vs multi-day regimens, different dose comparisons of same drug, active versus active and/or no treatment Only data relevant to metronidazole and/or tinidazole was included in the results.	adolescents, with confirmed *Trichomonas vaginalis* vaginitis		soreness, itching), side effects and complications of treatment	Two trials compared a single 2 g oral dose of metronidazole with a 5-7 day course of metronidazole. Parasitological cure was achieved in 88% and 92% of women with short and long treatments, respectively. Side effects were mainly gastrointestinal (nausea, vomiting) and more frequent with the single dose (15% vs 7%). In one trial with 468 women enrolled, only 38% attended the follow-up visit. Two studies compared a standard one week course of metronidazole with short course tinidazole and ornidazole, respectively. Overall, short treatment was comparable to long treatment in terms of no parasitological cure (relative risk [RR] 1.12, 95% confidence interval [CI] 0.58 to 2.16). Side effects, especially nausea/vomiting /dizziness were significantly more frequent with short treatment. Metronidazole was compared with tinidazole in 8 studies. Except for 1 study, all compared short regimens of each drug. There were no parasitological failures in 2 trials; however, a meta-analysis of all 8 studies results noted a statistically significant higher treatment failure rate (RR 3.24, 95% CI: 1.66 to 6.32), higher clinical failure rate (RR 3.81, 95% CI: 1.83 to 7.90), and higher side effect rate (RR 1.65, 95% CI: 1.35 to 2.02) with metronidazole. The author states that these results should be interpreted with caution as blind assessment of outcomes was reported in only 1 of 8 trials. There was no statistical difference in parasitological or clinical outcomes in this trial. The included trials showed that almost any nitroimidazole drug given as a single dose or over a longer period results in parasitological cure in 90% of cases. Oral single dose treatment with any nitroimidazole seems to be effective in achieving short term parasitological cure, but is associated with more frequent side effects than either longer oral or intravaginal treatment. Although rarely severe, side effects seem to be relatively common and dose related. It is not possible to conclude that tinidazole is more effective than metronidazole from the evidence reviewed. Outcome assessments were blinded in only one study that showed no difference between the two

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				drugs. Nitroimidazole drugs seem to be effective in achieving parasitological cure in short term follow-up. Partner treatment can be effective in decreasing longer term reinfection rates.
Miscellaneous				
Nelson et al.[94] (2011) Metronidazole, vancomycin, fusidic acid, nitazoxanide, teicoplanin, rifampin, rifaximin, bacitracin, fidaxomicin	MA Patients with *Clostridium difficile*-associated diarrhea (CDAD)	N=1,152 (15 trials) Variable duration	Primary: Initial resolution of diarrhea; initial conversion of stool to *C. difficile* cytotoxin or negative stool culture; recurrence of diarrhea; recurrence of *C. difficile* cytotoxin or positive stool culture; patient response to cessation of prior antibiotic therapy; emergent surgery; death	Primary: Only 3 of the 15 studies could be analyzed for direct comparison of metronidazole and vancomycin. There was no difference in symptomatic cure minus recurrences between the two medications (RR, 0.91; 95% CI, 0.81-1.03). Vancomycin was favored over bacitracin for symptomatic cure (RR, 0.58; 95% CI, 0.34-0.99) and bacteriologic initial response (RR, 0.52; 95% CI, 0.31-0.86). There was no difference in symptomatic recurrence. Teicoplanin was found to be more effective than vancomycin for: symptomatic cure of *C. difficile* (RR, 1.21, 95% CI, 1.00-1.46); bacteriologic initial response (RR, 1.43; 95% CI, 1.14-1.81); bacteriologic cure (RR, 1.82; 95% CI, 1.19-2.78). There was no difference in symptomatic initial response, symptomatic recurrence, or bacteriologic recurrence. There was no difference between fusidic acid and vancomycin in symptomatic initial response, symptomatic cure, bacteriologic initial response, bacteriologic cure, symptomatic recurrence or bacteriologic recurrence. There was no difference between nitazoxanide and vancomycin in symptomatic initial response, recurrence of diarrhea w/in 31 days or symptomatic cure. There was no difference between rifaximin and vancomycin in symptomatic initial response or bacteriologic initial response. There was no difference between metronidazole and nitazoxanide in initial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				resolution of diarrhea or recurrence of diarrhea at 31 days. There was no difference between metronidazole and metronidazole + rifampin in initial resolution of diarrhea or recurrence of diarrhea within 40 days. Teicoplanin was more effective than metronidazole for bacteriologic initial cure (RR, 0.76; 95% CI, 0.6-0.98); bacteriologic cure (RR, 0.76; 95% CI, 0.58-1.00). There was no difference between teicoplanin and metronidazole in outcome of symptomatic cure, initial symptomatic response, or symptomatic recurrence. There was no difference between metronidazole and fusidic acid in symptomatic initial response, symptomatic cure, bacteriologic initial cure, bacteriologic cure or symptomatic response. Teicoplanin was more effective than fusidic acid for symptomatic cure (RR, 1.36; 95% CI, 1.02-1.83); bacteriologic initial cure (RR, 1.68; 95% CI, 1.19-2.37); bacteriologic cure (RR, 1.73; 95% CI, 1.19-2.51). There was no difference between teicoplanin and fusidic acid in symptomatic initial response or symptomatic recurrence. There was no difference between high-dose and low-dose vancomycin or teicoplanin therapy for symptomatic initial response. There was no difference between high-dose and low-dose vancomycin, fidaxomicin, or teicoplanin therapy for symptomatic recurrence. There was no difference between high-dose and low-dose vancomycin or teicoplanin therapy for symptomatic cure. There was no difference between high-dose and low-dose vancomycin or teicoplanin therapy for bacteriologic cure.
Zar et al.[71]	RCT, DB, PC	N=172	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2007) Metronidazole 250 mg orally 4 times per day for 10 days vs vancomycin 125 mg orally 4 times per day for 10 days	Patients with *Clostridium difficile*-associated diarrhea (CDAD)	21 days	Clinical cure	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, respectively (P=0.02). Clinical symptoms recurred in 15% of the patients treated with metronidazole and 14% of those treated with vancomycin.
McFarland et al.[72] (2002) Metronidazole ≤1 g to 2 g PO per day; taper or pulse vs vancomycin ≤1 g to ≥2 g PO per day; taper, pulse, or combination with another agent	DB, PC, RCT 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 antibiotic treatment	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).
Bricker et al.[73] (2005) Metronidazole or bacitracin or fusidic acid* or teicoplanin* or rifaximin vs vancomycin	MA Patients with diarrhea who recently received antibiotics for an infection other than *C difficile*	N=582 Precise duration of therapy not specified	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*	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			cytotoxin and/or positive stool culture, patient response to cessation of prior antibiotic therapy	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.
Al-Nassir et al.[97] (2008) Metronidazole vs vancomycin	PRO, OBS Patients with *C. Difficile*-associated disease (CDAD)	N=82 13 days	Primary: Concentration of VRE overgrowth pre- and post-CDAD therapy Secondary: Rate of new VRE colonization	Primary: Vancomycin-treated patients were more likely to be in the ICU during therapy and there was a non-significant trend towards more concurrent antibiotic use in the vancomycin treatment arm. For patients with VRE colonization prior to study, there was no significant difference in length of therapy for vancomycin or metronidazole (11.2 vs 12.1 days, respectively; P=0.088). There was no significant difference among the groups in concentrations of VRE prior to therapy between or at 2 weeks posttreatment (P>0.35). At 21-25 days posttreatment, there was a significant decrease in VRE in both groups (P<0.049). For patients who were not colonized with VRE prior to study, new colonization of VRE in stool cultures occurred in 14% of metronidazole-treated courses and 8% of vancomycin-treated courses (P=1.0). No occult VRE infections occurred in patients with newly positive VRE stool cultures.
Al-Nassir et al.[98] (2008) Metronidazole vs vancomycin	PRO, OBS Patients with *C. Difficile*-associated disease (CDAD)	N=52 9 months	Primary: Time to resolution of diarrhea; time to undetectable levels of *C. difficile* in stool	Primary: More vancomycin-treated patients had previous CDAD (38.9% vs 2.9%, P=0.002) compared to metronidazole treated patients. A total of 29% of metronidazole-treated patients had therapy changed to vancomycin after 3-10 days due to persistent symptoms. Patients with a change in therapy were not more likely to be infected with a resistant strain of *C. difficile*. Patients with a change in therapy were more likely to be prescribed a proton-pump inhibitor or have continued use of other

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				antibiotics during *C. difficile* treatment. After 5 days, vancomycin- treated patients were more likely to have undetectable levels of *C. difficile* (HR, 3.99; 95% CI, 1.41-11.3; P=0.009). After 5 days, vancomycin-treated patients were more likely to have resolution of diarrhea (HR, 4.17; 95% CI, 1.53-11.4; P=0.005).
Ortiz et al.[100] (2001) Nitazoxanide 100 mg BID (ages 2-3 years) or 200 mg BID (ages 4-11 years) for 3 days vs metronidazole 125 mg BID (ages 2-5 years) or 250 mg BID (ages 6-11 years) for 5 days	PRO, RCT\ Children aged 2-11 years with acute diarrhea and cysts for *G. intestinali* within 7 days	N=110 7 days	Primary: Clinical response at 7 days Secondary: Parasitological response	Primary: There was no difference in the proportion of children with a clinical "well" response at 7 days between the nitazoxanide group (85%) and the metronidazole group (80%; P=0.6148). Secondary: There was no difference in the proportion of children with a parasitological response at 7 days between the nitazoxanide group (71%) and the metronidazole group, (75%; P=0.8307). The adverse events were similar between both groups and were mild in nature. Most were thought to be due to giardiasis.
Musher et al.[99] (2009) Nitazoxanide 500 mg every 12 hours vs vancomycin 125 mg orally every 6 hours	PRO, RCT, DB Patients with *C. difficile* (+) stool cultures with ≥3 loose stools/24 hours, and either: fever >35 C, abdominal pain, or leukocytosis	N=50 1 month	Primary: Clinical response at the end of treatment (10-13 days) Secondary: Time to resolution of symptoms; sustained response rate at 31 days	Primary: Response to treatment occurred in 74% of vancomycin-treated patients and 77% of nitazoxanide-treated patients (95% CI, -24% to 28%). Those that completed therapy had response rates of 87% in the vancomycin group and 94% in the nitazoxanide group (95% CI, -18% to 30%). Secondary: The time to resolution of all symptoms was similar in the 2 groups (P=0.55). Two patients treated with vancomycin and 1 patient treated with nitazoxanide had a relapse within 31 days. Sustained response rates in the ITT group were 67% in the vancomycin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group and 73% in the nitazoxanide group, (95% CI, -22% to 32%). Sustained response rates in patients that completed therapy were 78% in vancomycin-treated patients and 89% in nitazoxanide-treated patients (95% CI, -18% to 35%).
Solomkin et al.[92] (2009) Metronidazole 500 mg IV twice daily plus ceftriaxone 2 g IV once 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 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.[91] (2010)	RCT, MC, OL Patients ≥18 years	N=473 Up to 35 days	Primary: Clinical response in the clinically	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%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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 IV as an initial dose, followed by 50 mg IV every 12 hours for 4 to 14 days (TGC)	of age with community-origin complicated intra-abdominal infections (cIAIs)		evaluable (CE) population at the test-of-cure (TOC) visit Secondary: Bacteriological efficacy and safety	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%).
Kow et al.[93] (1995) Metronidazole 500 mg IV plus cefotaxime 1 g on induction of anesthesia vs cefoxitin 2 g IV on	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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				
Lewis[74] (2002) Metronidazole 2 g orally vs neomycin 2 g orally vs amikacin 1 g IV vs	RCT, PC, DB, 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 (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metronidazole 1 g IV vs placebo				
Song et al.[75] (1998) Metronidazole plus cefuroxime vs gentamicin plus metronidazole vs first or second generation cephalosporin vs third generation cephalosporin vs other agents as monotherapy or combination therapy	MA Surgical patients	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 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).
Lauritano et al.[103] (2009)	PRO, RCT, Patients with	N=142 7 days	Primary: Glucose breath test (GBT)	Primary: GBT normalization rate was significantly higher in the rifaximin group compared to the metronidazole group (63.5% vs 43.7%, respectively;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metronidazole 250 mg TID for 7 days vs rifamaxin 400 mg TID for 7 days	bloating, abdominal pain, flatulence or diarrhea for ≥6 months due to small intestine bacterial overgrowth (SIBO)		normalization rate Secondary: Adverse events	P<0.05). There were no significant differences in the per-protocol group. Secondary: The incidence of adverse events was significantly higher in the metronidazole group compared to the rifaximin group (22.5% vs 8.5%, respectively; OR, 1.59; 95% CI, 1.15-8.61). Five drop outs occurred in the metronidazole group due to adverse events compared to none in the rifaximin group.
Buranawarodomkul et al.[102] (1990) Tinidazole 2 g as a single dose vs metronidazole 500 mg BID for 7 days	PRO, OBS Female patients 15-45 years of age with non-specific vaginitis	N=171 1-2 weeks	Primary: Cure (defined as absence of symptoms and presence of <3 criteria)	Primary: After treatment, 8% of patients treated with metronidazole and 14% of patients treated with tinidazole had 3 or more symptoms. There was no statistical significant difference between metronidazole and tinidazole in patients with less than 3 symptoms (P=0.1688). In both groups, leukorrhea, itching, offensive odor and pelvic discomfort were all significantly reduced from pre- to posttreatment for both metronidazole and tinidazole (P<0.01 for both). There was no difference in posttreatment reduction of leukorrhea, itching, offensive odor, pelvic discomfort or dysuria when metronidazole was compared to tinidazole (P>0.05). Dysuria was not significantly reduced in the metronidazole group from pre- (8%) to posttreatment (2%; P=0.086). There was a significant difference in the incidence of adverse events between metronidazole (22%) and tinidazole (8%; P=0.025).

Drug regimen abbreviations: BID=twice daily, IV=intravenous, PCP=*Pneumocystis carinii* pneumonia, PO=oral, QD=once daily, SMX-TMP=sulfamethoxazole-trimethoprim, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk
Miscellaneous abbreviations: AIDS=acquired immunodeficiency virus, HIV=human immunodeficiency virus, TLAE=treatment limiting adverse events
*Product not commercially available in the United States.

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 12. Relative Cost of the Antiprotozoals, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Atovaquone	suspension	Mepron®	$$$$$	N/A
Metronidazole	capsule, injection, extended-release tablet, tablet	Flagyl®*, Flagyl ER®	$$$-$$$$	$
Nitazoxanide	suspension, tablet	Alinia®	$$$-$$$$$	N/A
Pentamidine	inhalation, injection	Nebupent®, Pentam 300®	$$$	N/A
Tinidazole	tablet	Tindamax®	$$$	N/A

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

X. Conclusions

The miscellaneous antiprotozoals are used to treat a variety of infectious diseases, including amebiasis, anaerobic bacterial infections, bacterial vaginosis, cryptosporidiosis, giardiasis, *Pneumocystis* pneumonia (PCP) and trichomoniasis.[1-11] Metronidazole is the only product that is available in a generic formulation.

Metronidazole, nitazoxanide and tinidazole are approved for the treatment of intestinal protozoa.[5-8,11] Guidelines recommend the use of metronidazole or tinidazole for the treatment of patients with amebiasis.[26-27,89,105] The majority of the clinical trials evaluating these agents were conducted in the 1970's and found that tinidazole was more effective than metronidazole.[30-32,34,36-39] However, metronidazole was only administered for 2 to 5 days.

Current dosing and consensus guidelines recommend the use of metronidazole for 10 days for the treatment of amebiasis. Nitazoxanide is recommended for the initial treatment of cryptosporidiosis in immunocompetent individuals, and it has been shown to be more effective than placebo in clinical trials.[41-44,77,89,105] Guidelines recommend the use of nitazoxanide or tinidazole for the initial treatment of giardiasis.[27,89,105] Metronidazole is considered an alternative treatment option due to the high frequency of gastrointestinal adverse events. The majority of the clinical trials have compared metronidazole with tinidazole and found that tinidazole was more effective.[30,48-51,53] However, metronidazole was only administered as a single dose. Current dosing and consensus guidelines recommend that metronidazole be administered for 5 days for the treatment of giardiasis.[89] Clinical trials that evaluated the use of metronidazole for 5 days demonstrated similar clinical response rates as nitazoxanide and tinidazole.[47,52]

Atovaquone is approved for the prevention and treatment of PCP in patients who are intolerant to sulfamethoxazole-trimethoprim.[4] Aerosolized pentamidine is approved for the prevention of PCP in high-risk, HIV-infected patients, and intravenous pentamidine is approved for the treatment of PCP (all patient types).[9-10] Guidelines recommend the initial use of sulfamethoxazole-trimethoprim for both the prevention and treatment of PCP.[20] Atovaquone and pentamidine are recommended as one of several alternative treatment options in patients who cannot tolerate sulfamethoxazole-trimethoprim.[20] Clinical trials have found that sulfamethoxazole-trimethoprim is more effective for the prevention of PCP than atovaquone or aerosolized pentamidine.[58,61-62,88] One study directly compared atovaquone and aerosolized pentamidine for the prevention of PCP and found that both agents were equally effective.[59] Another study directly compared atovaquone with intravenous pentamidine for the treatment of PCP and found that both agents were similar in efficacy.[55]

Metronidazole and tinidazole are approved for the treatment of bacterial vaginosis and trichomoniasis. Guidelines recommend the use of metronidazole or clindamycin for the initial treatment of bacterial vaginosis, and clinical trials have demonstrated similar outcomes with these agents.[18-19,21,28,80,82-87,89,90] Studies directly comparing metronidazole and tinidazole have also demonstrated similar cure rates.[67,96,102] For the treatment of trichomoniasis, guidelines recommend the use of metronidazole or tinidazole, and both agents have demonstrated similar efficacy in clinical trials.[18-19,21,29,64-66,89]

Metronidazole is approved for the treatment of a variety of other anaerobic bacterial infections. Guidelines recommend the use of metronidazole (alone or in combination with other anti-aerobic agents) for the treatment of *Clostridium difficile*-associated diarrhea, intra-abdominal infections, pelvic inflammatory disease, skin and soft-tissue infections and for surgical prophylaxis.[21-26,104]

There is insufficient evidence to support that one brand miscellaneous antiprotozoal agent is safer or more efficacious than another within its given indication. These agents may be considered first-line therapy in special circumstances. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous antiprotozoals 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 antiprotozoal 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Urinary Anti-infectives
AHFS Class 083600
May 9, 2012

I. Overview

The urinary anti-infectives are approved for the prophylaxis and treatment of urinary tract infections (UTIs), as well as for the relief of local symptoms associated with infections or caused by diagnostic procedures.[1-9] There are several single entity and combination products included in this review. Each of the agents has a unique mechanism of action and place in therapy.

Fosfomycin is a synthetic, broad spectrum antibacterial which inactivates the enzyme enolpyruvyl transferase, thereby inhibiting cell wall synthesis.[11-12] It is available as a single-dose sachet, which must be dissolved in water before oral administration.

Methenamine is hydrolyzed to formaldehyde in acidic urine, which is bactericidal against both gram-positive and gram-negative pathogens.[5] It is approved for the prophylaxis of recurrent urinary tract infections and should only be used after eradication of the infection by other appropriate antimicrobial agents. Methenamine may be used for prolonged periods of time because, unlike conventional antibiotics, acquired resistance does not appear to develop.[5] Methenamine is also available as a fixed-dose combination product which contains several ingredients to enhance the anti-infective properties and relieve symptoms associated with UTIs.[1-3] Methylene blue is a weak antiseptic, phenyl salicylate is a mild analgesic, and sodium phosphate helps to lower the pH in the urine.[1-3] Hyoscyamine is a parasympatholytic, which relaxes smooth muscle.

Nitrofurantoin is reduced to reactive intermediates by bacterial flavoproteins, which inhibits protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis and cell wall synthesis.[6-8] It is available in several formulations, including a monohydrate suspension, a macrocrystalline capsule, and a fixed-dose combination product. Nitrofurantoin macrocrystals are a larger crystal form of nitrofurantoin monohydrate, allowing for slower absorption and less excretion.[7] The fixed-dose combination product contains 25% macrocrystalline nitrofurantoin and 75% nitrofurantoin monohydrate. The monohydrate component forms a gel matrix upon exposure to gastric and intestinal fluids, which releases nitrofurantoin over time.[8]

Trimethoprim binds to and reversibly inhibits dihydrofolate reductase and blocks the production of tetrahydrofolic acid, which interferes with bacterial biosynthesis of nucleic acids and proteins.[9] It is approved for the treatment of uncomplicated UTIs and may also be used for the treatment of acute otitis media.[9] Trimethoprim is also available in a fixed-dose combination with sulfamethoxazole, which was previously reviewed with the sulfonamides (AHFS 081220) and is not included in this review.

The urinary anti-infectives that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The majority of the products are available in a generic formulation. This class was last reviewed in November 2009.

Table 1. Urinary Anti-infectives Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Fosfomycin	packet	Monurol®	none
Methenamine	tablet	Hiprex®*	methenamine
Methenamine, methylene blue, phenyl salicylate, sodium phosphate, and hyoscyamine	capsule, tablet	Urelle®, Urin D.S.®*, UTA®, Utira C®*	methenamine, methylene blue, phenyl salicylate, sodium phosphate, and hyoscyamine
Methenamine and sodium phosphate	tablet	Uroqid-Acid No.2®	none
Methenamine, sodium phosphate, methylene blue, and hyoscyamine	tablet	N/A	methenamine, sodium phosphate, methylene blue, and hyoscyamine

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Nitrofurantoin	suspension	Furadantin®*	nitrofurantoin
Nitrofurantoin macrocrystals	capsule	Macrodantin®*	nitrofurantoin macrocrystals
Nitrofurantoin and nitrofurantoin macrocrystals	capsule	Macrobid®*	nitrofurantoin and nitrofurantoin macrocrystals
Trimethoprim	solution, tablet	Primsol®	trimethoprim

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

The urinary anti-infectives 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 urinary anti-infectives 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 anti-infective therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected. There is no information available regarding the microorganisms that are susceptible to the methenamine combination products.[1-3]

Table 2. Microorganisms Susceptible to the Urinary Anti-infectives[1-9]

Organism	Fosfomycin	Methenamine	Nitrofurantoin	Nitrofurantoin Macrocrystals	Nitrofurantoin/ Nitrofurantoin Macrocrystals	Trimethoprim
Gram-Positive Aerobes						
Enterococcus species		✔	✔	✔		
Enterococcus faecalis	✔					
Staphylococcus species		✔				✔
Staphylococcus aureus			✔	✔		
Streptococcus pneumoniae						✔
Staphylococcus saprophyticus					✔	✔
Gram-Negative Aerobes						
Enterobacter species			✔	✔		✔
Escherichia coli	✔	✔	✔	✔	✔	✔
Haemophilus influenzae						✔
Klebsiella species			✔	✔		
Klebsiella pneumoniae						✔
Proteus mirabilis						✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the urinary anti-infectives are summarized in Table 3.

Table 3. Treatment Guidelines Using the Urinary Anti-infectives

Clinical Guideline	Recommendation(s)
American Academy of Pediatrics (AAP)/American Academy of Family Physicians (AAFP): **Diagnosis and Management of Acute Otitis Media[14] (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)/European Society for Microbiology and Infectious Diseases (ESCMID): **International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women[17] (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-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

Clinical Guideline	Recommendation(s)
	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**[15] **(2008)**	• For uncomplicated acute bacterial cystitis, recommended treatment regimens are as follows:
	  ○ Trimethoprim–sulfamethoxazole: 1 tablet (160 mg trimethoprim–800 mg sulfamethoxazole) twice daily for 3 days
	  ○ Trimethoprim 100 mg twice daily for 3 days
	  ○ 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
	  ○ Nitrofurantoin macrocrystals 50-100 mg 4 times daily or nitrofurantoin monohydrate 100 mg twice daily for 7 days
	  ○ Fosfomycin tromethamine, 3-g dose (powder) single dose.

Infectious Diseases Society of America (IDSA): **Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults**[16] **(2005)**	• Pyuria is not an indication for antimicrobial treatment because treatment has not been shown to decrease the frequency of symptomatic infection or the risk of developing hypertension, chronic kidney disease, or genitourinary cancer; it also has not been shown to improve length of survival. • Treatment for asymptomatic bacteriuria in premenopausal, nonpregnant women is not recommended because treatment has not been shown to decrease the frequency of symptomatic infection or the

Clinical Guideline	Recommendation(s)
	risk of developing hypertension, chronic kidney disease, or genitourinary cancer, or to improve length of survival. • Treatment should be initiated in pregnant women with bacteriuria, as they are at increased risk of developing pyelonephritis and have a higher prevalence of premature delivery and infants of low birth weight. Antibiotic treatment is recommended for 3-7 days. • In the following special populations, treatment is not indicated for asymptomatic bacteriuria: catheterized patients, diabetic women, institutionalized and noninstitutionalized elderly patients, and persons with spinal cord injury. • To prevent bacteremia and sepsis, patients who have undergone traumatic genitourinary procedures associated with mucosal bleeding should be treated for asymptomatic bacteriuria. Antibiotic treatment should be initiated shortly before the procedure and continued only if the patient remains catheterized. • Treatment may be considered in asymptomatic catheterized women with persistent bacteriuria after 48 hours of catheter removal.
Infectious Diseases Society of America (IDSA): **Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults[10] (2009)**	• Methenamine salts should not be used to reduce catheter-associated bacteriuria (CA-bacteriuria) or catheter-associated urinary tract infections (CA-UTI) in patients with long-term intermittent or long-term indwelling urethral or supra-pubic catheterization. • There is insufficient data to make recommendations regarding methenamine salts to decrease CA-UTI in patients with condom catheters. • Methenamine salts may be used to reduce CA-bacteriuria or CA-UTI in gynecologic surgery patients catheterized for less than 1 week. • There is no data to recommend one methenamine salt over another. • Target urinary pH should be <6.0 when using methenamine salts.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the urinary anti-infectives are noted in Tables 4-5. 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 Urinary Anti-infectives (Drugs F-M)[1-9]

Indications	Fosfomycin	Methenamine	Methenamine/ Methylene Blue/ Phenyl Salicylate/ Sodium Phosphate/ Hyoscyamine	Methenamine/ Sodium Phosphate	Methenamine/ Sodium Phosphate/ Methylene Blue/ Hyoscyamine
Prophylactic or suppressive treatment of frequently recurring urinary tract infections		✔		✔	
Relief of local symptoms associated with urinary tract infections			✔		✔
Relief of urinary tract symptoms caused by diagnostic procedures			✔		✔
Treatment of uncomplicated urinary tract infections	✔				✔
Treatment of symptoms of irritative voiding			✔		

Table 5. FDA-Approved Indications for the Urinary Anti-infectives (Drugs N-T)[1-9]

Indications	Nitrofurantoin	Nitrofurantoin Macrocrystals	Nitrofurantoin/ Nitrofurantoin Macrocrystals	Trimethoprim
Acute otitis media				✔
Treatment of urinary tract infections	✔	✔	✔	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the urinary anti-infectives are listed in Table 6.

Table 6. Pharmacokinetic Parameters of the Urinary Anti-infectives[1-9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Fosfomycin	34-58	0	none	Renal (38) Feces (18)	5.7
Methenamine	Not reported	Not reported	Liver (10-25)	Renal (90)	4.3
Nitrofurantoin	87-94	90	Not reported	Renal (34-40)	0.3-1
Nitrofurantoin macrocrystals	87-94	90	Not reported	Renal (20-25)	0.3-1
Nitrofurantoin and nitrofurantoin macrocrystals	40	90	Not reported	Renal (20-25)	Not reported
Trimethoprim	Not reported	44	Liver (10-20)	Renal (50-60) Feces (<4)	8-10

V. Drug Interactions

Significant drug interactions with the urinary anti-infectives are listed in Table 7.

Table 7. Significant Drug Interactions with the Urinary Anti-infectives[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Trimethoprim	1	Dofetilide	Elevated dofetilide plasma concentrations may occur with increased risk of ventricular arrhythmias, including torsades de pointes.
Trimethoprim	1	Methotrexate	Trimethoprim may increase the risk of methotrexate-induced bone marrow suppression and megaloblastic anemia.
Methenamine	2	Sulfonamides	Methenamine is contraindicated for use with sulfonamides due to the potential for formation of insoluble precipitates in the urine.
Trimethoprim	2	ACE inhibitors	Severe hyperkalemia has been reported with concurrent use of ACE inhibitors and trimethoprim.
Trimethoprim	2	Dapsone	Increased serum levels of dapsone and trimethoprim may occur, possibly increasing the pharmacologic and toxic effects of each drug.
Trimethoprim	2	Hydantoins	Serum hydantoin concentrations may be increased, producing an increase in the pharmacologic and toxic effects of hydantoins.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the urinary anti-infectives are listed in Tables 8-9.

Table 8. Adverse Drug Events (%) Reported with the Urinary Anti-infectives (Drugs F-M)[1-9]

Adverse Events	Fosfomycin	Methenamine	Methenamine/ Methylene Blue/ Salicylate/ Sodium Phosphate/ Hyoscyamine	Methenamine/ Sodium Phosphate	Methenamine/ Sodium Phosphate/ Methylene Blue/ Hyoscyamine
Central Nervous System					
Confusion	-	-	-	✔	-
Dizziness	1-2	-	✔	✔	✔
Fatigue	<1	-	-	✔	-
Fever	<1	-	-	-	-
Headache	4-10	-	-	✔	-
Insomnia	<1	-	-	-	-
Malaise	-	-	-	✔	-
Migraine	<1	-	-	-	-
Nervousness	<1	-	-	-	-
Paresthesia	<1	-	-	-	-
Seizures	-	-	-	✔	-
Somnolence	<1	-	-	-	-
Dermatological					
Pruritus	<1	<4	-	-	-
Rash	1.4	<3.5	-	✔	-
Skin disorder	<1	-	-	-	-
Gastrointestinal					
Abdominal pain	2.2	-	-	-	-
Abnormal stools	<1	-	-	-	-
Anorexia	<1	-	-	-	-
Constipation	<1	-	-	-	-
Diarrhea	9-10	-	-	✔	-
Dyspepsia	1-2	-	-	-	-
Flatulence	<1	-	-	-	-
Nausea	4-5	<3.5	✔	✔	✔
Toxic megacolon	✔	-	-	-	-
Vomiting	<1	<3.5	✔	✔	✔
Xerostomia	<1	-	✔	-	✔

Adverse Events	Fosfomycin	Methenamine	Methenamine/ Methylene Blue/ Salicylate/ Sodium Phosphate/ Hyoscyamine	Methenamine/ Sodium Phosphate	Methenamine/ Sodium Phosphate/ Methylene Blue/ Hyoscyamine
Genitourinary					
Albuminuria	-	✔	-	-	-
Dysuria	<1	<3.5	✔	✔	✔
Hematuria	<1	<1	-	✔	-
Menstrual disorder	<1	-	-	-	-
Urinary retention	-	-	✔	-	✔
Vaginitis	6-8	-	-	-	-
Musculoskeletal					
Asthenia	1	-	-	-	-
Back pain	3	-	-	-	-
Muscle cramps	-	-	-	✔	-
Myalgia	<1	-	-	-	-
Respiratory					
Asthma exacerbation	✔	-	-	-	-
Dyspnea	-	-	✔	✔	✔
Pharyngitis	2.5	-	-	-	-
Pulmonary hypersensitivity reactions	✔	-	-	-	-
Rhinitis	4.5	-	-	-	-
Shortness of breath	-	-	✔	-	✔
Other					
ALT increased	<1	✔	-	-	-
Anaphylaxis	✔	-	-	-	-
Angioedema	✔	-	-	-	-
Aplastic anemia	✔	-	-	-	-
Blurred vision	-	-	✔	-	✔
Bone/joint pain	-	-	-	✔	-
Cholestatic jaundice	✔	-	-	-	-
Dysmenorrhea	2.6	-	-	-	-
Ear disorder	<1	-	-	-	-
Flu syndrome	<1	-	-	-	-
Flushing	-	-	✔	-	✔
Hearing loss	✔	-	-	-	-
Hepatic necrosis	✔	-	-	-	-
Lymphadenopathy	<1	-	-	-	-

Adverse Events	Fosfomycin	Methenamine	Methenamine/ Methylene Blue/ Salicylate/ Sodium Phosphate/ Hyoscyamine	Methenamine/ Sodium Phosphate	Methenamine/ Sodium Phosphate/ Methylene Blue/ Hyoscyamine
Numbness/tingling	-	-	-	✔	-
Optic neuritis	✔	-	-	-	-
Pain	2.2	-	-	✔	-
Swelling of feet/lower legs	-	-	-	✔	-
Tachycardia	-	-	✔	✔	✔
Weakness of extremities	1-2	-	-	✔	-
Weight gain	-	-	-	✔	-

✔ Percent not specified
- Event not reported

Table 9. Adverse Drug Events (%) Reported with the Urinary Anti-infectives (Drugs N-T)[1-9]

Adverse Events	Nitrofurantoin	Nitrofurantoin Macrocrystals	Nitrofurantoin/ Nitrofurantoin Macrocrystals	Trimethoprim
Cardiovascular				
Chest pain	✔	✔	✔	-
EKG changes	✔	✔	✔	-
Intracranial hypertension	✔	✔	✔	-
Central Nervous System				
Aseptic meningitis	-	-	-	✔
Chills	✔	✔	<1	-
Confusion	✔	✔	✔	-
Depression	✔	✔	✔	-
Dizziness	✔	✔	<1	-
Drowsiness	✔	✔	<1	-
Fever	✔	✔	<1	✔
Headache	✔	✔	6	-
Nystagmus	✔	✔	✔	-
Peripheral neuropathy	✔	✔	✔	-
Psychotic reactions	✔	✔	✔	-
Vertigo	✔	✔	✔	-
Dermatological				
Alopecia	✔	✔	<1	-
Eczematous eruptions	✔	✔	✔	-
Erythema multiforme	✔	✔	✔	✔

Adverse Events	Nitrofurantoin	Nitrofurantoin Macrocrystals	Nitrofurantoin/ Nitrofurantoin Macrocrystals	Trimethoprim
Erythematous eruptions	✔	✔	✔	-
Exfoliative dermatitis	✔	✔	✔	✔
Maculopapular eruptions	✔	✔	✔	-
Phototoxic eruptions	-	-	-	✔
Pruritus	✔	✔	<1	✔
Rash	-	-	-	3-6
Stevens-Johnson syndrome	✔	✔	✔	✔
Toxic epidermal necrosis	-	-	-	✔
Urticaria	✔	✔	<1	-
Gastrointestinal				
Abdominal pain	✔	✔	<1	<1
Anorexia	✔	✔	✔	-
C. difficile associated diarrhea	✔	✔	✔	-
Constipation	✔	✔	<1	-
Diarrhea	✔	✔	<1	4.2
Dyspepsia	✔	✔	<1	-
Epigastric distress	-	-	-	✔
Flatulence	-	-	1.5	-
Nausea	✔	✔	8	✔
Pseudomembranous colitis	✔	✔	✔	-
Vomiting	✔	✔	<1	✔
Hematologic				
Agranulocytosis	✔	✔	✔	-
Aplastic anemia	✔	✔	✔	-
Eosinophilia	✔	✔	✔	✔
G6PD deficiency anemia	✔	✔	✔	-
Granulocytopenia	✔	✔	✔	-
Hemolytic anemia	✔	✔	✔	-
Leukopenia	✔	✔	✔	✔
Megaloblastic anemia	✔	✔	✔	✔
Methemoglobinemia	-	-	✔	✔
Neutropenia	-	-	-	✔
Thrombocytopenia	✔	✔	✔	✔
Hepatic				
Cholestatic jaundice	✔	✔	✔	✔
Hepatic necrosis	✔	✔	✔	-
Hepatitis	✔	✔	✔	-

Adverse Events	Nitrofurantoin	Nitrofurantoin Macrocrystals	Nitrofurantoin/ Nitrofurantoin Macrocrystals	Trimethoprim
Laboratory Test Abnormalities				
ALT increased	✔	✔	✔	✔
AST increased	✔	✔	✔	✔
BUN increased	-	-	-	✔
Hemoglobin decreased	✔	✔	✔	-
Hyperkalemia	-	-	-	✔
Hyperphosphatemia	✔	✔	✔	-
Hyponatremia	-	-	-	✔
Serum creatinine increased	-	-	-	✔
Musculoskeletal				
Arthralgia	✔	✔	✔	-
Asthenia	-	-	✔	-
Malaise	-	-	<1	-
Myalgia	✔	✔	✔	-
Respiratory				
Cough	✔	✔	✔	-
Cyanosis	✔	✔	✔	-
Dyspnea	✔	✔	✔	-
Pleural effusion	✔	✔	✔	-
Pulmonary fibrosis	✔	✔	-	-
Pulmonary hypersensitivity reactions	✔	✔	<1	-
Pulmonary infiltration	✔	✔	✔	-
Other				
Amblyopia	-	-	<1	-
Anaphylaxis	✔	✔	✔	✔
Hypersensitivity reactions	✔	✔	✔	-
Optic neuritis	✔	✔	✔	-
Pancreatitis	✔	✔	✔	-
Sialadenitis	✔	✔	✔	-

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the urinary anti-infectives are listed in Table 10.

Table 10. Usual Dosing Regimens for the Urinary Anti-infectives[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Fosfomycin	Urinary Tract Infections: One 3 g sachet mixed with water before ingesting	Safety and efficacy in children <12 years of age have not been established.	Packet: 3 g
Methenamine	Prophylaxis/Suppression of Recurring Urinary Tract Infections: 1 g twice daily	Prophylaxis/Suppression of Recurring Urinary Tract Infections: 6-12 years of age: 0.5 to 1 g twice daily ≥12 years of age: 1 g twice daily	Tablet: 500 mg 1 g
Methenamine, methylene blue, phenyl salicylate, sodium phosphate, and hyoscyamine	Urinary Tract Discomfort: 1 tablet or capsule four times daily	Safety and efficacy in children <6 years of age have not been established. For children ≥6 years of age, the dosage should be individualized by the physician.	Capsule: 120 mg-10 mg-36 mg-40.8 mg-0.12 mg Tablet: 81 mg-0.12 mg 81.6 mg-10.8 mg-40.8 mg-36.2 mg-0.12 mg
Methenamine and sodium phosphate	Prophylaxis/Suppression of Recurring Urinary Tract Infections: Initial: 2 tablets 4 times daily; Maintenance: 2-4 tablets daily in divided doses	Safety and efficacy in children have not been established.	Tablet: 500 mg-500 mg
Methenamine, sodium phosphate, methylene blue, and hyoscyamine	Urinary Tract Discomfort: 1 tablet four times daily	Safety and efficacy in children <12 years of age have not been established. For children ≥12 years of age, the dosage should be individualized by the physician.	Tablet: 81.6 mg-40.8 mg-10.8 mg-0.12 mg
Nitrofurantoin	Long-Term Suppressive Therapy: 50-100 mg at bedtime Urinary Tract Infections: 50 to 100 mg 4 times daily for 1 week or for at least 3 days after sterility of the urine is obtained.	Long-Term Suppressive Therapy ≥1 month of age:1 mg/kg per 24 hours given in a single dose or two divided doses Urinary Tract Infections: ≥1 month of age: 5-7 mg/kg per 24 hours given in 4 divided doses for 1 week, or for at least 3 days after sterility of the urine is obtained	Suspension: 25 mg/5 ml
Nitrofurantoin macrocrystals	Long-Term Suppressive Therapy: 50-100 mg at bedtime	Long-Term Suppressive Therapy ≥1 month of age:1 mg/kg per 24 hours given in a	Capsule: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Urinary Tract Infections: 50 to 100 mg 4 times daily for 1 week or for at least 3 days after sterility of the urine is obtained.	single dose or two divided doses Urinary Tract Infections: ≥1 month of age: 5-7 mg/kg per 24 hours given in 4 divided doses for 1 week, or for at least 3 days after sterility of the urine is obtained	
Nitrofurantoin and nitrofurantoin macrocrystals	Urinary Tract Infections: 100 mg every 12 hours for 7 days	Urinary Tract Infections: ≥12 years of age: 100 mg every 12 hours for 7 days	Capsule: 100 mg
Trimethoprim	Urinary Tract Infections: 100 mg every 12 hours or 200 mg every 24 hours for 10 days	Acute Otitis Media: ≥6 months of age:10 mg/kg per 24 hours, given in divided doses every 12 hours for 10 days	Solution: 50 mg/5 ml Tablet: 100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the urinary anti-infectives are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Urinary Anti-infectives

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Urinary Tract Infections (Complicated)				
Senol et al.[53] (2010) Fosfomycin (FT) 3 g every other night for 3 doses vs meropenem (M)1 g IV every 8 hours or imipenem-cilastatin (IC) 500 mg IV every 6 hours for 14 days	OBS, PRO Adults with extended-spectrum beta-lactamase-producing *E. Coli*-related complicated lower urinary tract infections (ESBL)	N=47 31 days	Primary: Clinical success (resolution of symptoms); microbiologic success (sterile cultures 7-9 days after treatment); relapse (isolation of ESBL-producing *E. Coli* in the control urine cultures); reinfection (isolation of any pathogen in the control urine cultures performed 28-31 days after the start of therapy)	Primary: Clinical and microbiological success in the FT and carbapenem group were similar (19/20 vs 21/27 and 16/20 vs 16/27, respectively; P>0.05). Relapse rates were similar between the FT and carbapenem group (1/16 vs 1/16, respectively; P>0.05). Reinfection rates were similar between the FT and carbapenem group (1/16 vs 1/16, respectively; P>0.05). In a subgroup of patients with indwelling catheters, the microbiologic success (87.5% vs 50%; P>0.079) and clinical success (100% vs 79%, P>0.05) was higher in the carbapenem group compared to the FT group; however, the differences did not reach statistical significance.
Urinary Tract Infections (Recurrent)				
Cronberg et al.[36] (1987) Methenamine hippurate 1 g BID vs placebo	XO, DB, RCT Women aged 40-80 years with recurrent acute cystitis	N=21 1 to 2 years	Primary: Effectiveness of methenamine hippurate, with and without extra fluid intake, in preventing acute cystitis	Primary: In 27 patient years (14 patients completed 1 year and 13 patients completed both years), 52 attacks of cystitis due to reinfection occurred, which included 11 in patients receiving methenamine and 41 in patients taking placebo. Methenamine hippurate reduced the incidence of acute cystitis by 73%. There were 2.1 infection per patient/year with placebo vs 0.8 with methenamine hippurate (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treatments were interchanged every 6 months for 2 years				There was no difference between patients taking extra fluid and normal fluid (28 vs 24 attacks, respectively) and extra fluid did not reduce the efficacy of methenamine (6 vs 5 attacks).
Peterson et al.[37] (1986) Methenamine hippurate 0.5 g BID	PRO Females 5 to 12 years of age with recurrent UTIs	N=20 12 months	Primary: Number of infections per patient per year	Primary: Number of infections per patient per year was 3.1 before treatment with methenamine hippurate and 0.7 during treatment (P<0.001). After prophylaxis was stopped, the number of infections per patient per year increased to 1.4 (P<0.05, as compared to incidence of infection during treatment). There were several complaints regarding taste; however, no side effects were observed overall.
Banovac et al.[38] (1978) Methenamine 1 g BID vs no antimicrobial therapy	PRO, OL Hospitalized patients with spinal cord injury and neurogenic bladder dysfunction treated with intermittent catheterization	N=56 Variable duration	Primary: Frequency of UTIs based on weekly urinalysis and urine culture	Primary: Patients treated with methenamine had 23.4% positive urine cultures compared to 57.5% in the untreated control group (P<0.001).
Lee et al.[24] (2007) Methenamine vs placebo or no treatment	MA At-risk populations for UTI including, renal tract calculi, women following gynecological operations, men undergoing prostate operations, pregnant women, premenopausal women,	N=2,032 (13 RCT) 5 days to 6 months	Primary: Symptomatic UTI and positive urine culture, quantitative urine culture, adverse reactions	Primary: Six studies (654 patients) reported symptomatic UTI and eight studies (796 patients) reported bacteriuria. Overall, study quality was mixed. The overall pooled estimates for the major outcome measures were not interpretable because of underlying heterogeneity. The evaluation of symptomatic bacteria involved six studies: RR 0.53 (95% CI 0.24 to 1.18). The tests of heterogeneity was significant (P=0.003). The sensitivity analysis did not reveal any difference in overall effect when missing urine tests were assumed to be positive (RR 0.53, 95% CI 0.24 to 1.17) The evaluation of bacteruria analysis involved eight studies: RR 0.67

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	postmenopausal women, spinally injured males, recurrent UTI			(95% CI 0.45 to 0.99). The Q test was significant using a random effects model indicating heterogeneity (P=0.0002). Subgroup analyses suggested that methenamine hippurate may have some benefit in patients without renal tract abnormalities (symptomatic UTI: RR 0.24, 95% CI 0.07 to 0.89; bacteriuria: RR 0.56, 95% CI 0.37 to 0.83), but not in patients with known renal tract abnormalities (symptomatic UTI: RR 1.54, 95% CI 0.38 to 6.20; bacteriuria: RR 1.29, 95% CI 0.54 to 3.07). For short-term treatment duration (1 week or less) there was a significant reduction in symptomatic UTI in those without renal tract abnormalities (RR 0.14, 95% CI 0.05 to 0.38). The rate of adverse events was low. Nausea was the most common symptom and was noted in 12 patients from a total of six studies.
Bourque et al.[44] (1956) Methenamine mandelate 1 g TID to QID vs no antimicrobial therapy	CS, OS Patients admitted to the hospital for urological study	N=100 Duration not specified	Primary Effectiveness based on nature of the condition, on the infecting organism, and in relation to duration, urinary pH, and side effects	Primary Seventy-one cases were chronic infections and 29 were common, acute urinary infections. Of the chronic cases, 41% had complete urine sterilization, 21% had partial sterilization, and 38% showed no bacteriological change. Of the acute cases, 59% had complete sterilization, 24% had partial sterilization, and 17% showed no bacteriological change. The efficacy result was lowest at 33% for cases infected by streptococci. Efficacy rates ranged between 50% and 100% for all other infecting organisms. The shortest period in which urine was completely sterilized was 3 days, and the longest was 28 days. Methenamine mandelate demonstrated 80% effectiveness in acidic urine. There were 2 reports of burning on micturition and 2 reports of gastric distress.
Kevorkian et al.[45] (1984)	PC Patients with	N=39 Duration not	Primary Development of infection during	Primary Fifty-three percent of patients receiving methenamine mandelate (9/17) became infected compared to 86% in the placebo group (19/22; P<0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Methenamine mandelate vs placebo	neurogenic bladder dysfunction in a program of intermittent catheterization and bladder retraining	specified	trial	
Vainrub et al.[46] (1977) Methenamine mandelate 1 g and ascorbic acid 1 g every 6 hours vs no antimicrobial therapy	PRO Paraplegic or quadriplegic inpatient men on the spinal cord unit with previously documented episodes of urinary infection who currently had an indwelling catheter or had one at some point in the past	N=32 5 days	Primary CFU per milliliter, leukocytes (WBC) per milliliter, and pH for patients who had indwelling Foley or suprapubic catheters, and for those who were on a program of intermittent straight catheterization	Primary There was no significant difference between before and during treatment results for CFU and WBC per milliliter (P>0.7) or pH (P>0.3).
Olsen et al.[42] (1983) Methenamine hippurate 1 g BID for 6 days vs cefotaxime 750 mg at the start of the operation, then BID for 5 days	RCT Men aged 52-90 years with urinary tract infection and benign prostatic hyperplasia undergoing transurethral prostatic resection	N=42 6 days	Primary: Clinical and bacteriological efficacy	Primary: Postoperative temperature elevation (greater than 38ºC) occurred in 1 of the 22 patients in the cefotaxime group (4.5%), and in 9 of the 20 in the methenamine hippurate group (45%; P<0.05). Fifty-nine percent of patients in the cefotaxime group responded to treatment (13/22 patients) compared to 5% in the methenamine hippurate group (1/20 patients; P<0.005).
Brumfitt et al.[39] (1991) Methenamine	RCT Female patients suffering from	N=99 Up to 1 year	Primary: Number of patients experiencing no symptomatic	Primary: Fifty-eight percent of patients receiving nitrofurantoin remained free of symptoms compared to 27% of patients receiving methenamine hippurate.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hippurate 1 g every 12 hours vs nitrofurantoin 50 mg every 12 hours	recurrent urinary infections		episodes by monthly microbiological and clinical response	Ninety-one percent of nitrofurantoin-treated patients remained abacteriuric while on therapy vs 67% of methenamine-treated patients. Twenty-eight percent of patients discontinued nitrofurantoin therapy compared to 3.5% of patients receiving methenamine. Nausea was the most frequently occurring adverse event in the nitrofurantoin group compared to the methenamine group.
Kasanen et al.[40] (1982) Methenamine hippurate vs nitrofurantoin vs trimethoprim vs placebo	RCT, PC Patients with recurrent UTIs	N=290 1 year	Primary: Recurrence of UTIs	Primary: UTIs recurred in 63.2% of patients given placebo compared to 34.2% of patients receiving methenamine hippurate, 25% of patients receiving nitrofurantoin, and 10.4% of patients treated with trimethoprim. Adverse events were mild and occurred most commonly in patients receiving nitrofurantoin (13.9% vs 2.9% with placebo, 4.1% with methenamine hippurate, and 3.9% with trimethoprim. Patients who withdrew were in the nitrofurantoin group (1.4%) or methenamine hippurate group (2.7%).
Kuhlemeier et al.[41] (1985) Methenamine hippurate 1 g BID vs nitrofurantoin macrocrystals 50 mg TID	MC Male hospitalized patients, free of indwelling catheters, with spinal cord injury who had experienced at least 1 bout of bacteriuria	N=161 Duration not specified	Primary: Prevention of future bacteriuria	Primary: There was no statistically significant difference between all agents in preventing bacteriuria (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs SMX-TMP 400 mg-80 mg BID vs nalidixic acid 500 mg QID vs ascorbic acid 1 g QID				
Pfau et al.[51] (1992) Nitrofurantoin macrocrystals 50 mg single-dose vs cephalexin 250 mg single-dose	PRO Pregnant women with a history of UTIs (and, in some instances, pyelonephritis) for postcoital prophylaxis	N=33 5 to 11 months	Primary: Incidence of UTIs	Primary: UTIs (130) occurred before prophylaxis (mean duration of observation: 7 months) compared to only a single UTI occurring during pregnancy post-prophylaxis. Both nitrofurantoin macrocrystals and cephalexin reached high bacterial concentrations in the urinary tract and induced minimal to zero resistance in the introital gram-negative bacterial flora.
Raz et al.[52] (1991) Nitrofurantoin 50 mg QD for 6 months vs norfloxacin 200 mg QD for 6 months	PRO Women aged ≥16 years with a history of ≥3 documented episodes of UTI during the last 6 months	N=102 6 months	Primary: Clinical bacteriological infections (defined as the isolation of an organism in quantitative counts of $>10^5$ CFU/mL; presence of dysuria, frequency or urgency, and/or	Primary: Urine samples were sterile in 70.7% of patients treated with nitrofurantoin and 92.4% of patients treated with norfloxacin (P<0.005); 65% of patients receiving nitrofurantoin remained free of symptoms compared to 81% of women receiving norfloxacin (P=0.05). The incidence of UTIs after initiation of prophylaxis decreased from 3 episodes per 6 months before nitrofurantoin treatment to 0.03 episodes per 6 months after prophylaxis; and the incidence of UTIs decreased from 3.1 episodes per 6 months before norfloxacin treatment to 0.02 episodes per 6 months after prophylaxis (P<0.005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			suprapubic tenderness), drug-related side effects	Side effects occurred in 15% of women receiving norfloxacin and 17% of women given nitrofurantoin, with more severe effects reported with nitrofurantoin treatment (4 patients discontinued treatment).
Brumfitt et al.[47] (1985) Nitrofurantoin macrocrystals 100 mg QD for 12 months vs trimethoprim 100 mg QD for 12 months	RCT Patients with history of at least 3 UTIs within the previous 12 months	N=72 12 months	Primary: Symptomatic attacks, bacteriuria	Primary: Mean interval between symptomatic attacks from the pretreatment period was increased threefold while on either nitrofurantoin macrocrystals or trimethoprim treatment. Fifty-nine percent of patients receiving nitrofurantoin macrocrystals remained abacteriuric and asymptomatic throughout treatment vs 24% receiving trimethoprim (P<0.05). Treatment with nitrofurantoin macrocrystals was more effective at preventing bacteriuria compared with trimethoprim (P<0.05). Resistance was noted at a rate of approximately 5% per month in patients given trimethoprim, whereas no resistance occurred in patients given nitrofurantoin macrocrystals. Patients receiving nitrofurantoin macrocrystals reported more side effects compared to those receiving trimethoprim (40% vs 18.4%, respectively; P<0.05).
Bendstrup et al.[48] (1990) Nitrofurantoin 1-1.5 mg/kg QD vs trimethoprim 2-3 mg/kg QD	DB, MC, RCT Children aged 1 to 14 years with recurrent UTIs and urinary tract abnormalities	N=130 5 to 6.5 months	Primary: UTI-free periods demonstrated by actuarial percentage recurrence-free curves	Primary: In patients with abnormal urography and/or reflux, nitrofurantoin was associated with greater prophylaxis efficiency (P=0.0025); but there was no difference between nitrofurantoin and trimethoprim for prophylaxis in patients without urinary abnormalities. Following prophylaxis, there was no difference in actuarial percentage recurrence-free curves between the two groups (P=0.92). Patients receiving trimethoprim for prophylaxis were found to have 76% trimethoprim-resistant bacteria during prophylaxis, as compared to 8% before (P<0.0001) and 17% after prophylaxis (P<0.0001). Nitrofurantoin did not alter the pattern of resistance or bacteriological constellation. Side effects were reported in 37% of patients receiving nitrofurantoin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				versus 21% receiving trimethoprim (P=0.05); nitrofurantoin-treated patients most commonly reported GI symptoms.
Stamm et al.[49] (1980) Nitrofurantoin macrocrystals 100 mg QD vs trimethoprim 100 mg QD vs SMX-TMP 200/40 mg QD vs placebo	DB, PC Women with history of UTI in preceding year	N=60 6 months	Primary: Infections per patient year	Primary: Infections per patient-year were comparable in patients receiving nitrofurantoin macrocrystals (0.14), trimethoprim (0), or SMX-TMP (0.15), and occurred more frequently in the placebo group (2.8; P<0.001 for placebo versus each treatment regimen). Infections were more likely to develop following prophylaxis in women who had had 3 or more infections in the year prior to prophylaxis (P<0.005). Infections with pathogens other than *E coli* occurred more frequently following prophylaxis (P<0.05).
Goettsch et al.[50] (2004) Nitrofurantoin vs trimethoprim vs norfloxacin	RETRO Women aged 15 to 65 years who received a first course (3, 5, or 7 days) of trimethoprim, nitrofurantoin or norfloxacin	N=16,703 Up to 31 days after the end of the initial treatment	Primary: Failure of initial treatment (defined by the need for additional treatment)	Primary: Over 14% of total patients required a new prescription within 31 days after the end of initial treatment. Treatment failures were seen in 18.9% in patients who received a 3-day course of nitrofurantoin and 15.6% in patients who received a 3-day course of trimethoprim. Five days of treatment with nitrofurantoin macrocrystals, trimethoprim, or norfloxacin resulted in failure rates of 13.1%, 13.2%, and 12.3%, respectively. Norfloxacin for 7 days demonstrated an 8.5% failure rate.
Rajkumar et al.[22] (1988)	PRO Children with	N=112 10 days	Primary: Cure (absence of significant	Primary: The cure rate was 100% for patients treated with trimethoprim compared to 100% for the SMX-TMP group (P>0.05), 93% for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Trimethoprim 10 mg/kg QD for 10 days vs SMX-TMP 40-8 mg/kg QD for 10 days vs sulfamethoxazole 150 mg/kg QD for 10 days vs ampicillin 100 mg/kg QD for 10 days	repeated colony counts of greater than 100,000 CFU/mL of the same organism grown in 2-3 consecutive clean catch specimens		bacterial growth at end of treatment), failure (persistence of pathogens during therapy), relapse (regrowth of same organism within 28 days), recurrence (positive growth 28 days after therapy onset), side effects	sulfamethoxazole group (P<0.05), and 63% for the ampicillin group (P<0.01). The trimethoprim and SMX-TMP groups had no failures whereas the sulfamethoxazole and ampicillin groups had a 7% (P<0.05) and 37% (P<0.01) rate of failure, respectively. Relapses occurred in 4% of the trimethoprim-treated patients whereas the SMX-TMP group had a 7% relapse rate (P>0.05); sulfamethoxazole and ampicillin groups were not associated with any relapses. The trimethoprim group had 7% recurrence compared to 6% with SMX-TMP, 4% with sulfamethoxazole and 7% with ampicillin (P>0.05). GI side effects and skin rashes were not encountered in the trimethoprim group; white blood cell (WBC) depression was the lowest in the trimethoprim group.
Brumfitt et al.[18] (1972) Trimethoprim 200 mg every 12 hours for 7 days vs SMX-TMP 800 mg-160 mg every 12 hours for 7 days vs ampicillin 1 g every 12 hours for 7 days	PRO Pregnant patients with bacteriuria, hospitalized patients, and patients in general practice	N=96 6 weeks	Primary: Cure rates	Primary: In pregnancy, the cure rates were equal (85%) with trimethoprim and SMX-TMP, 65% with ampicillin, and 78% with cephalexin (P value not significant). In hospitalized patients, there was no significant difference in cure rates between the various treatment groups, which were 73% with trimethoprim, 84% with SMX-TMP, 67% with ampicillin, and 62% with cephalexin. In general practice, trimethoprim was associated with a 96% cure rate compared to 81% in the SMX-TMP group, 89% in the ampicillin group, and 62% in the cephalexin group. Results for cephalexin were significantly lower than the other groups (P<0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs cephalexin 1 g every 12 hours for 7 days				
Urinary Tract Infections (Uncomplicated)				
Estebanez et al.[55] (2009) Fosfomycin 3 g as a single dose vs amoxicillin-clavulanate 500 mg every 8 hours for 7 days	PRO Pregnant women with asymptomatic bacteruria (AB)	N=109 End of pregnancy	Primary: Microbiologic cure (defined by sterilized urine culture) Secondary: Rate of reinfection, recurrence, persistence, adverse events, and compliance	Primary: Microbiologic cure occurred in 80.37% of the amoxicillin-clavulanate group and 83.01% in the fosfomycin group (RR, 1.195; 95% CI, 0.451-3.165; P=0.72). Secondary: There was one reinfection in the fosfomycin group and eight in the amoxicillin-clavulanate group (RR, 0.13; 95% CI, 0.02-0.81; P=0.045). There was one recurrence in each group (RR, 1.06; 95% CI, 0.11-10.12; P=0.96). Five patients had persistent infections in the fosfomycin group versus 2 in the amoxicillin-clavulanate group (RR, 2.64; 95% CI, 0.59-11.79; P=0.39). One patient in the fosfomycin group and 11 patients in the amoxicillin-clavulanate group experienced adverse events (RR, 0.10; 95% CI, 0.01-0.72; P=0.008). There were 5 cases of non-compliance with amoxicillin-clavulanate and none with fosfomycin (RR, 0.00; 95% CI, 0.00-0.81; P=0.076).
Usta et al.[54] (2011) Fosfomycin 3 g as a single dose (FT) vs cefuroxime 500 mg	RCT Pregnant women ≥12 weeks gestation with uncomplicated lower UTIs (bacteriuria and/or pyuria and positive urine culture)	N=90 2 weeks	Primary: Clinical success (defined as resolution of symptoms); microbiologic cure	Primary: There was no significant difference in clinical success rates between the treatment groups after 2 weeks. Clinical success rates were 78.6%, 77.8%, and 86.2% for the FT, AC and CA groups, respectively (P=NS). Microbiologic cure rates were 82.1%, 81.5% and 89.7% in the FT, AC and CA groups, respectively (P>0.05). Compliance was significantly higher in the FT group (100%) compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
twice daily for 5 days (CA) vs amoxicillin-clavulanate 625 mg twice daily for 5 days (AC)				to the AC (77.8%) or CA (82.8%) (P<0.05). The most common adverse event was diarrhea with an incidence of 10.7% in the FT group, 11.1% in the AC group and 6.9% in the CA group. There was no significant difference between the groups with respect to adverse events.
Elhanan et al.[31] (1994) Fosfomycin 3 g as a single-dose vs cephalexin 500 mg QID for 5 days	RCT Women ≥16 years of age with acute uncomplicated cystitis (symptoms of dysuria, frequency/urgency of urination, absence of fever/flank pain, pyuria, $\geq 10^5$ CFU/mL of an organism sensitive to both antibiotics)	N=112 5 days to 1 month	Primary: Clinical cure, microbiological cure	Primary: At the 5 day follow-up, 91% of patients receiving fosfomycin and 91% of patients receiving cephalexin were considered clinically cured (P=NS); at 1 month, 86% and 78% were considered cured, respectively (P=NS). In terms of microbiological cure, 91% of fosfomycin-treated patients compared to 83% of cephalexin-treated patients were cured at 5 days; 81% of fosfomycin-treated patients compared to 68% of cephalexin-treated patients were cured at 1 month.
Stein et al.[25] (1999) Fosfomycin 3 g as a single-dose vs nitrofurantoin monohydrate/ macrocrystals 100 mg capsules BID for 7 days	DB, RCT Females ≥12 years of age with symptoms of acute uncomplicated UTI	N=749 6 weeks	Primary: Bacteriologic response (cure, failure, relapse, or reinfection), clinical response (cure, improvement, or failure) at each visit	Primary: The bacteriologic cure rate at visit 2 (5 to 11 days after initial treatment dose) was 78.1% with fosfomycin and 86.3% with nitrofurantoin (P=0.02); at visit 3 (5 to 11 days after last day of medication) the cure rate was 86.9% with fosfomycin and 80.9% with nitrofurantoin (P=0.17); at visit 4 (4 to 6 weeks after last day of medication) the cure rate was 96% with fosfomycin and 91.1% with nitrofurantoin (P=0.18). There were no statistically significant differences between fosfomycin and nitrofurantoin in terms of clinical outcomes at any visit (P=0.3 to 0.91). Most commonly occurring adverse drug reactions (ADRs) in the fosfomycin group were diarrhea (2.4%), vaginitis (1.8%), and nausea

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(0.8%). The most common ADRs with nitrofurantoin were nausea (1.6%), vaginitis (1.6%), dizziness (0.8%), and diarrhea (0.8%). Seven patients in the fosfomycin group discontinued therapy (1.9%) vs 16 patients receiving nitrofurantoin (4.3%).
Van Pienbrook et al.[26] (1993) Fosfomycin 3 g as a single-dose vs nitrofurantoin 50 mg QID for 7 days	DB, MC, RCT Patients with acute, uncomplicated cystitis (acute dysuria, stranguria, and/or urinary frequency)	N=231 42 days	Primary: Clinical cure rates (resolution of symptoms based on patient's judgment), bacteriological cure rates at 4, 9, and 42 days after treatment start	Primary: No difference in clinical cure rates was seen between fosfomycin-treated patients and nitrofurantoin-treated patients at day 4 (94% vs 95%, respectively), day 9 (95% vs 94%, respectively), or at day 42 (82% vs 80%, respectively; P>0.05 for all). Bacteriological assessments, based on difference in dipslide results at follow-up visits were not significant. By day 4, 43% of patients receiving fosfomycin reported side effect(s) versus 25% of patients given nitrofurantoin (P=0.00); most common adverse events were gastrointestinal (GI) complaints and were generally mild. At day 9, there was no difference in the incidence of side effects between fosfomycin and nitrofurantoin groups (20% vs 16%, respectively; P=NS).
Ferraro et al.[30] (1990) Fosfomycin 3 g as a single-dose vs norfloxacin 400 mg BID for 7 days	OL, RCT Elderly patients with uncomplicated lower UTI	N=60 Up to 25-35 days	Primary: Clinical resolution rate, bacteriological resolution rate	Primary: Clinical and bacteriological resolution rates were 76.6% for patients treated with fosfomycin and 73.3% for patients treated with norfloxacin (P>0.05).
Naber et al.[28] (1992) Fosfomycin 3 g as a single-dose vs	RCT, MC, SB Urine cultures of women with acute uncomplicated cystitis	N=349 7 days	Primary: Eradication of baseline pathogens based on urine culture	Primary: At 1 week, baseline pathogens were eradicated in 87.1% of fosfomycin-treated patients, 88.9% of SMX-TMP-treated patients, and 86.4% of ofloxacin-treated patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SMX-TMP 1.92 g single-dose vs ofloxacin 200 mg single-dose				
Naber et al.[29] (1990) Fosfomycin 3 g as a single-dose vs SMX-TMP 1.92 g single-dose vs ofloxacin 200 mg single-dose	RCT, SB Female patients with acute uncomplicated UTI	N=562 4 weeks	Primary: Clinical improvement based on amount of baseline bacteriuria	Primary: Clinical improvement for patients with significant bacteriuria was seen in 94.7% of patients receiving fosfomycin, 94% of patients receiving SMX-TMP, and 95.4% of patients given ofloxacin at up to 1 week. Clinical improvement was seen in 81.9% of patients receiving fosfomycin, 79.4% of patients receiving SMX-TMP, and 80.8% of patients given ofloxacin at up to 4 weeks. Clinical improvement for patients with low count bacteriuria was demonstrated in 95.2% of patients receiving fosfomycin, 96.4% of patients receiving SMX-TMP, and 93.7% of patients given ofloxacin. In patients with no bacteriuria, clinical improvement was possible in 81.8% of patients given fosfomycin, 100% of patients taking SMX-TMP, and 100% of patients taking ofloxacin.
Davis et al.[27] (1990) Fosfomycin 3 g as a single-dose vs trimethoprim 200 mg single-dose	DB, DD, RCT Non-pregnant adult women with symptoms of UTI (frequency, dysuria)	N=55 6 weeks	Primary: Bacteriological eradication, recurrence, reinfection, persistence of infection	Primary: Patients receiving fosfomycin demonstrated 77.3% eradication of infection compared to 54.5% of patients treated with trimethoprim. Nine percent of fosfomycin-treated patients vs 4.5% of nitrofurantoin-treated patients had recurrence. Nine percent of fosfomycin-treated patients vs 4.5% of nitrofurantoin-treated patients had reinfection. Persistence was noted in 5% of fosfomycin-treated patients compared to 36% of trimethoprim-treated patients.
Iravani et al.[32]	DB, MC, PRO, RCT	N=713	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1999) Nitrofurantoin monohydrate/ macrocrystals 100 mg twice daily for 7 days vs SMX-TMP 800/160 mg tablets twice daily for 7 days vs ciprofloxacin 100 mg tablets twice daily for 3 days	Women ≥18 years of age with primary diagnosis of acute, symptomatic, uncomplicated UTI; confirmed by a positive urine culture within 48 hours of study onset, signs and symptoms of dysuria, pyuria, and urinary frequency for <10 days	Up to 6 weeks	Pathogen eradication after 4-10 days of therapy, clinical response rate (resolution of symptoms), relapse rate, adverse events	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).
Hooten et al.[33] (1995) Nitrofurantoin macrocrystals 100 mg QID for 3 days vs SMX-TMP 800/160 mg BID for 3 days vs amoxicillin 500 mg TID for 3 days vs	PRO, RCT Women with acute uncomplicated cystitis	N=149 6 weeks	Primary: Cure, persistence of bacteriuria	Primary: At 6 weeks, the cure rate was 82% in patients treated with SMX-TMP, 61% in patients treated with nitrofurantoin (P=0.04 vs SMX-TMP), 67% in patients given amoxicillin (P=0.11 vs SMX-TMP), and 66% in patients treated with cefadroxil (P=0.11 vs SMX-TMP). Persistence of significant bacteriuria was seen with 3% of patients receiving SMX-TMP, 16% of patients receiving nitrofurantoin (P=0.05 vs SMX-TMP), 14% of patients given amoxicillin (P=0.11 vs SMX-TMP), and 0% in patients receiving cefadroxil. Adverse events were seen in 43% of patients receiving nitrofurantoin, 35% of patients receiving SMX-TMP, 25% of patients given amoxicillin, and 30% in patients receiving cefadroxil.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cefadroxil 500 mg BID for 3 days				
Gupta et al.[43] (2007) Nitrofurantoin monohydrate/ macrocrystals 100 mg twice daily for 5 days vs SMX-TMP 800-160 mg tablets twice daily for 3 days	RCT, OL Women18 to 45 years of age who were not pregnant, who were in good general health, and 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<.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<.001).
Kasanen et al.[34] (1981) Trimethoprim 160 mg BID for 7 days vs cephalexin 500 mg BID for 7 days	MC, RCT Patients with acute UTIs	N=241 6 weeks	Primary: Resolution of UTI, recurrence of UTI	Primary: Three days after discontinuation of treatment, 98.3% of patients receiving trimethoprim demonstrated resolution of UTI compared to 82.1% of patients given cephalexin. UTI recurred in 15.2% of trimethoprim-treated patients and 30.9% of cephalexin-treated patients after 6 weeks (P<0.025).
Newsom et al.[35]	PRO	N=40	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1986) Trimethoprim 200 mg BID for 5 days vs ciprofloxacin 100 mg BID for 5 days	Elderly patients with UTIs	5 days	Clinical and microbiological outcome at day 5	During ciprofloxacin therapy all patients had sterile urine and 5 days later only 1 patient had reinfection with *E coli*. In the trimethoprim group, the urine did not clear and only in 1 patient and was found to be a resistant organism.
Miscellaneous				
Falagas et al.[56] (2010) Fosfomycin vs other antibiotics	MA Patients with microbiologically confirmed cystitis or suspicion of cystitis	N=1,657 (27 trials) 1 day to 18 months posttreatment	Primary: Clinical success (defined as complete cure and/or non-complete [improvement] resolution of symptoms Secondary: Microbiologic success (defined as eradication); microbiologic relapse; microbiologic reinfection; adverse events	<u>Non-pregnant females</u> Primary: There was no difference in clinical success among patients treated with fosfomycin compared to other treatments (RR, 1.00; 95% CI, 0.96-1.03). Secondary: There was no difference in microbiological success, microbiologic relapse or microbiologic reinfection among patients treated with fosfomycin compared to other treatments. There was no difference in adverse events or study withdrawal rates. <u>Non-pregnant females and males</u> Primary: There was no difference in clinical success among patients treated with fosfomycin compared to other treatments (RR, 0.98; 95% CI, 0.87-1.11). Secondary: There was no difference in microbiological success rates among the treatment groups (RR, 1.01; 95% CI, 0.88-1.17). There was no difference in adverse events or study withdrawal rates. <u>Pregnant females</u> Primary: There was insufficient data to analyze the primary outcome.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: There was no difference in microbiological success rates among the treatment groups (RR, 1.00; 95% CI, 0.96-1.05). Pregnant women had fewer adverse events in the fosfomycin group versus all comparators (RR 0.35, 95%CI=0.12-0.97). <u>Pediatric patients</u> Primary: There was insufficient data to analyze the primary outcome. Secondary: There was no difference in microbiological success rates among the treatment groups (RR, 0.98; 95% CI, 0.92-1.05). There was no difference in adverse events or study withdrawal rates. <u>Other considerations</u> There was no difference in microbiological success between single-dose fosfomycin and single-dose comparator regimens. There was no difference in microbiological success between single-dose fosfomycin and longer comparator regimens.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: CO=cross-over, CS=case studies, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PRO=prospective, RT=randomized trial, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind
Miscellaneous abbreviations: ADR=adverse drug reaction, CFU=colony-forming units, GI=gastrointestinal, SMX-TMP=sulfamethoxazole and trimethoprim combination product, UTI=urinary tract infection

Additional Evidence

Dose Simplification
Trimethoprim administered as a single dose, or over the course of 7 days, was evaluated in female patients with symptoms of lower urinary tract infection and positive bacteriuria.[19] Short-term efficacy was 82% for single-dose therapy and 94% for the 7-day regimen (P<0.001). Accumulated efficacy was 71% for single-dose and 87% for 7-day therapy (P<0.001). Adverse events were noted less frequently with single-dose therapy; however, this was not significant. van Merode et al. evaluated microbiological and clinical cure rates with trimethoprim administered over 3 days or 5 days in women with UTIs.[20] There was no significant difference in bacteriological cure rates between the 3-day and 5-day treatment regimens. After completing the 3-day regimen, 44% of women considered themselves "not recovered" due to persistence of symptoms compared with 35% of women receiving the 5-day treatment (P>0.05).

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 Urinary Anti-infectives

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Fosfomycin	packet	Monurol®	$$$$	N/A
Methenamine	tablet	Hiprex®*	$$$$	$-$$$
Methenamine, methylene blue, phenyl salicylate, sodium phosphate, and hyoscyamine	capsule, tablet	Urelle®, Urin D.S.®*, UTA®, Utira C®*	$$$$	$
Methenamine and sodium phosphate	tablet	Uroqid-Acid No.2®	$$	N/A
Methenamine, sodium phosphate, methylene blue, and hyoscyamine	tablet	N/A	N/A	$$
Nitrofurantoin	suspension	Furadantin®*	$$$$	$$$$
Nitrofurantoin macrocrystals	capsule	Macrodantin®*	$$	$-$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Nitrofurantoin and nitrofurantoin macrocrystals	capsule	Macrobid®*	$$$	$$
Trimethoprim	solution, tablet	Primsol®	$$	$

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

X. Conclusions

The urinary anti-infectives are approved for the prophylaxis and treatment of urinary tract infections (UTIs), as well as for the relief of local symptoms associated with infections or caused by diagnostic procedures.[1-9] Trimethoprim solution is also approved for the treatment of otitis media. There are several single entity and combination products available; each of the agents has a unique mechanism of action and place in therapy. The majority of the products are available in a generic formulation.

For the treatment of uncomplicated UTIs, guidelines recommend trimethoprim (with or without sulfamethoxazole), nitrofurantoin, fosfomycin, or a quinolone as initial therapy.[15,17] Methenamine can be used for the treatment of catheter-associated bacteriuria and UTIs in gynecologic surgery patients who are catheterized for less than 1 week.[10] However, it should not be used to reduce the risk of bacteriuria or UTIs in patients with long-term intermittent or long-term indwelling catheters.

Clinical trials have demonstrated comparable efficacy among the urinary anti-infectives for the prophylaxis and treatment of UTIs.[25-27,41,48-49] Relatively few studies have demonstrated greater efficacy with one agent over another.[39-40,47] The urinary anti-infectives have also been shown to be comparable in efficacy to anti-infective agents in other classes.[18,22,28-32,43,53-56] There were no studies found in the medical literature that evaluated the efficacy and safety of the methenamine combination products.

There is insufficient evidence to support that one brand urinary anti-infective 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 urinary anti-infectives 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 urinary anti-infective 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.

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