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Drug Class Update: Antifungals (oral and topical)

Month/Year of Review: November 2019

Date of Last Review: September 2014 (topical)

July 2015 (oral)

Literature Search: 07/15/14 – 08/15/19

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update: The purpose of this update is to review and evaluate new high-quality literature that has been published since the last review on oral and topical antifungal therapies as well as evaluate appropriateness of current policy and preferred drug list (PDL) placement.

Research Questions:

- Is there any new comparative evidence related to efficacy for the oral or topical antifungals for important outcomes (e.g., clinical cure or mortality)?
- Is there any new comparative evidence based on harms outcomes for the oral or topical antifungals?
- Are there any subpopulations which would receive more benefit or suffer more harm from specific oral or topical antifungals?

Conclusions:

- Four systematic reviews and meta-analyses, five guidelines and one randomized trial are included in this update.
- The risk of developing and risk of dying from cryptococcal disease was reduced with primary prophylaxis antifungal therapy, itraconazole or fluconazole, in human immunodeficiency virus (HIV)-positive individuals at high risk of developing cryptococcal disease based on moderate quality evidence from one Cochrane review.¹
- Evidence for the use of topical antifungals for seborrheic dermatitis was insufficient to draw strong conclusions regarding efficacy or safety.²
- One fair-quality trial found isavuconazole to be noninferior to voriconazole for the outcome of mortality at day 42 when used in patients with invasive mold disease caused by aspergillosis or other filamentous fungi.³
- Guidance for the treatment of opportunistic infections in adult and adolescent patients with HIV, guidelines on the management of aspergillosis, clinical practice guideline for the treatment of coccidioidomycosis, guidance on the management of candidiasis, and prevention and treatment of cancer-related infections supports current antifungal preferred drug list (PDL) placement.^{4,5,6,7,8}
- There is insufficient evidence on benefits or harms of antifungals in subpopulations.

Recommendations:

- No changes to the PDL are recommended based on a review of the clinical safety and efficacy evidence.
- After evaluation of costs in executive session, no PDL changes were recommended.

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Summary of Prior Reviews and Current Policy

- Previous reviews have not found clinically significant differences in efficacy or harms between the different oral antifungals.
- Prior authorization is required for griseofulvin, itraconazole, and terbinafine due to limited usage beyond onychomycosis, which is unfunded.
- Use of voriconazole is authorized for use by hematologists, oncologists and infectious disease without restriction to allow for coverage of invasive aspergillosis.
- Evidence does not support differences in harms or adverse events between the oral antifungals with the exception of ketoconazole which has been associated with hepatotoxicity, adrenal insufficiency and drug interactions.
- There is no evidence of clinically significant differences in efficacy or harms between the topical antifungal treatments.
- The Oregon Health Plan list of prioritized services does not fund treatment for candidiasis of mouth, skin and nails or dermatophytosis of nail, groin, scalp and foot and other dermatomycosis in immune-competent hosts. Topical antifungal agents are solely indicated for these and other related non-funded conditions.
- Financial impact of this class is minimal to the Oregon Health Plan (OHP) and there was 98% utilization of preferred oral antifungals and 83% of preferred topical therapies in the second quarter of 2019.

Background:

The antifungal class covers treatment of life-threatening illnesses, such as invasive aspergillosis, to unfunded cosmetic diagnoses such as toenail onychomycosis. Serious fungal infections are usually seen in individuals with compromised immune systems, such as prolonged neutropenia, allogeneic hematopoietic stem cell transplant and acquired immunodeficiencies requiring oral or intravenous antifungal therapy.⁵ Topical antifungals are used for treatment of dermatophytes, yeasts and molds involving the skin, scalp, nails and mucous membrane. The most common skin infection is tinea pedis followed by tinea corporis and tinea capitis.⁹ Important outcomes to determine antifungal efficacy include: symptom improvement, clinical cure (clinical symptoms), mycological cure (negative mycological test) and mortality.

Antifungals can be categorized as azoles, echinocandins, polyenes, allylamines and flucytosine.¹⁰ Choice of antifungal depends on indication, causative organism and resistance patterns. Caspofungin, anidulafungin and micafungin are echinocandins with similar spectrum of action but differing dosing and drug interaction profiles. Echinocandins are most commonly used for serious fungal infections such as invasive candidiasis and as empiric therapy in patients with neutropenic fever.¹¹ Additionally, echinocandins have been used for salvage therapy in patients with invasive aspergillosis. Amphotericin deoxycholate, liposomal amphotericin and nystatin are polyene antifungals. Because high risk of nephrotoxicity is associated with systemic formulations of polyenes, these therapies are therefore designated as second-line options for invasive aspergillosis and candidiasis infections. Allylamine antifungals consist of naftifine and terbinafine. Flucytosine has antifungal properties that can be used in combination with amphotericin B for severe cryptococcal pneumonia and meningoencephalitis, with a limited role in select invasive candidiasis infections. Due to high levels of resistance, flucytosine is not commonly used as monotherapy.¹² Drug interactions are common with antifungals and concomitant medications should be considered upon initiation.

Azole antifungals are categorized as either triazoles or imidazoles (e.g., fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole and ketoconazole). The azole antifungals are effective in treating several types of fungal infections: candidiasis, aspergillosis, cryptococcosis, histoplasmosis, blastomycosis, and coccidioidomycosis. Fluconazole is most commonly recommended first-line for a majority of fungal infections due to efficacy and tolerability. Of the azole antifungals, posaconazole and isavuconazole have the broadest spectrum of action and are not associated with nephrotoxicity. There is wide variability in the bioavailability and types of drug interactions (highly metabolized via cytochrome P450 enzyme system) between the different antifungals. Gastrointestinal issues

are the most common adverse reactions associated with antifungal therapy and hepatic manifestations from mild elevations to hepatic failure have been demonstrated. For these reasons, transaminase monitoring is recommended for patients receiving extended treatment with antifungal therapy. Drug monitoring is recommended for itraconazole, voriconazole, and posaconazole to ensure efficacy and avoid toxicity. For the initial treatment and salvage therapy triazole antifungals, such as voriconazole, are recommended for the treatment of aspergillosis.⁵

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane – Primary Antifungal Prophylaxis for Cryptococcal Disease in HIV-positive People

A systematic review and meta-analysis of the efficacy and safety of primary prophylaxis for cryptococcal disease in people who are HIV-positive was completed in 2018.¹ Patients were considered at high risk of cryptococcal disease with low cluster of differentiation 4 (CD4) cell counts. A total of nine trials, six of which were placebo controlled, met the inclusion criteria. Treatments included the antifungals itraconazole and fluconazole. Only two of the trials were conducted after the introduction of modern HIV treatments.¹ Overall the risk of bias was low for most of the trials for most of the domains.

Primary prophylaxis with antifungal therapy did not provide a conclusive all-cause mortality benefit due to the low quality of evidence. The risk of developing cryptococcal disease was reduced with antifungal therapy compared to placebo (RR 0.29; 95% CI, 0.17 to 0.49) based on moderate evidence. This finding equates to 30 per 1000 patients at risk of cryptococcal disease compared to 9 per 1000 patients receiving antifungal prophylaxis.¹ The risk of mortality due to cryptococcal disease was reduced in patient receiving antifungal prophylaxis from 3 per 1000 people treated with antifungals to 11 per 1000 people in those not receiving prophylaxis (RR 0.29; 95% CI, 0.11 to 0.72).¹ There was moderate evidence that of no difference in the discontinuation rates between antifungals and placebo. In conclusion, there was a benefit of primary prophylaxis with antifungals in patients at high risk of cryptococcal disease compared to placebo and in patients not receiving modern HIV treatment.

Cochrane – Topical Antifungals for Seborrhoeic Dermatitis

A 2015 Cochrane review evaluated the efficacy and safety of the use of topical antifungals for seborrhoeic dermatitis. Fifty-one studies of adolescents and adults (n=9052) were included. Most trial durations were five weeks or less and evaluated the following antifungals: ketoconazole (usually 2%), ciclopirox, lithium, bifonazole (not available in the US) and clotrimazole.

Most of the evidence for antifungal use in the treatment of seborrhoeic dermatitis is of low or very low quality due to the availability of only a few small studies. The use of topical ketoconazole was associated with similar remission rates as topical steroids (low quality of evidence), however, the adverse events were 44% lower in the ketoconazole group (RR 0.56; 95% CI, 0.32 to 0.96; number needed to benefit [NNTB] 3).² In general ketoconazole was more effective than placebo in reducing erythema and clearance of scaling; however, results could not be pooled. Results for ketoconazole compared to placebo were similar when studies with and without conflict of interest were analyzed separately. The use of topical ciclopirox 1% resulted in a reduction in the number of failed remissions compared to placebo at four weeks based on data from eight studies, 66% versus 79% (RR 0.79; 95% CI, 0.67 to 0.94), and adverse reactions were similar between therapies (moderate evidence).² In conclusion, there is insufficient evidence to draw strong conclusions on comparative efficacy or safety for the use of topical antifungals for seborrhoeic dermatitis.

After review, 7 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

Centers for Disease Control, National Institutes of Health, Human Immunodeficiency Virus Medicine Association of the Infectious Disease Society of America – Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

An updated version of guidance for managing opportunistic infections in patients with HIV was released in October of 2017.⁴ The guidelines include a comprehensive review of preventing and treating a multitude of infections; however, this review will focus on diseases in which antifungals are indicated. Recommendations are included for the management of candidiasis (mucocutaneous), coccidioidomycosis, and cryptococcosis. Recommendations are based on a systematic review of the literature with subsequent determination of the strength of the recommendation and quality of evidence used for the recommendation and are presented in **Table 1**.¹³

Table 1. Recommendation Strength and Quality Definitions⁴

Strength of Recommendation	Quality of Evidence for the Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	III: Expert opinion

Recommendations for antifungal treatment are indication dependent (**Table 2**).⁴ Oral fluconazole is the drug of choice for oropharyngeal candidiasis and esophageal candidiasis based on fungal clearance rates and lower recurrence rate. Oral fluconazole is also recommended first-line for vulvovaginal candidiasis. In treatment-resistant cases of mucocutaneous candidiasis, posaconazole oral suspension (AI), oral itraconazole (BII), anidulafungin (BII), caspofungin (BII), micafungin (BII), voriconazole (BII) or amphotericin B (BII) can be used.⁴ If secondary prophylaxis (i.e., maintenance/suppressive therapy) is indicated, oral fluconazole or posaconazole therapy are recommended. Topical therapy is recommended for patients who are pregnant (AIII), as systemic antifungal treatments range from pregnancy category B to X. Treatment of coccidioidomycosis can usually be treated with an oral triazole antifungal. Due to high relapse rates of approximately 80% of patients with coccidioidal meningitis, life-long antifungal therapy is indicated. For patients that are pregnant with non-meningeal

coccidioidomycosis, amphotericin B, deoxycholate or lipid preparation are recommended (AIII). Systemic azole antifungals should be avoided in the first trimester of pregnancy (BIII).⁴

Table 2. Antifungal Treatment Recommendations for Opportunistic Infections in Patients with HIV⁴

Indication for Therapy	Recommendation	Strength of Evidence
Oropharyngeal Candidiasis Duration of therapy: 7-14 days	Fluconazole 100 mg tablets or solution once daily*	A1
	Miconazole 50 mg mucoadhesive buccal tablets once daily	B1
	Clotrimazole troches 10 mg five times a day	B1
	Nystatin suspension or pastilles four times daily	BII
	Itraconazole 200 mg oral solution daily	B1
	Posaconazole 400 mg oral suspension twice daily for one day and then 400 mg daily	B1
Esophageal disease Duration of therapy: 14-21 days	Fluconazole 100 mg (up to 400 mg) once daily (oral or IV)*	A1
	Itraconazole oral solution 200 mg daily*	A1
	Oral itraconazole capsules (capsules not recommended due to variable absorption)	CII
	Isavuconazole 200 mg orally as a loading dose, followed by 50 mg daily	B1
	Isavuconazole 400 mg orally as a loading dose, followed by 100 mg daily	B1
	Isavuconazole 400 mg orally once weekly	B1
	Voriconazole 200 mg PO or IV twice daily	B1
	Amphotericin B deoxycholate IV daily	B1
	Lipid formulation of amphotericin B IV daily	BIII
	Echinocandins (caspofungin, micafungin, and anidulafungin) (doses not provided)	B1
Vulvovaginal Candidiasis Duration of therapy: fluconazole – 1 day, all others 3-7 days	Oral fluconazole 150 mg for one dose*	AII
	Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole)*	AII
	Itraconazole 200 mg oral solution	BII
Coccidioidomycosis Duration of therapy: depends on response Mild infections	Fluconazole 400 mg daily*	BII
	Itraconazole 200 mg twice daily*	BII
	Voriconazole 200 mg twice daily, after loading dose of 400 mg twice daily	BIII
	Posaconazole 300 mg delayed release tablets after loading dose of 300 mg twice daily for one day	BIII
	Posaconazole oral suspension 400 mg orally twice daily	BII
Bone or joint infections	Itraconazole 200 mg orally twice daily*	A1
	Fluconazole 400 mg orally once daily	B1
Severe infections	Lipid formulation of amphotericin B IV*	AIII
	Amphotericin B deoxycholate IV*	AII
Meningeal Infection	Fluconazole 400-800 mg daily (oral or IV)*	AII
	Itraconazole 200 mg orally 2-3 times daily	BII

	Voriconazole 200-400 mg orally twice daily after loading dose	BIII
	Posaconazole delayed release tablet loading dose of 300 mg twice daily on day one and then 300 mg daily	CIII
	Posaconazole oral suspension 400 mg orally twice daily	CIII
	Intrathecal amphotericin B when triazole antifungals are not effective	AIII
Cryptococcosis Induction therapy Duration of therapy: at least 2 weeks	Liposomal amphotericin B IV plus flucytosine*	AI
	Amphotericin B deoxycholate IV plus flucytosine*	AI
	Amphotericin B lipid complex IV plus flucytosine	BII
	Liposomal amphotericin B IV plus fluconazole	BIII
	Amphotericin B (deoxycholate) IV plus fluconazole	BI
	Liposomal amphotericin B IV	BI
	Amphotericin B deoxycholate IV	BI
	Fluconazole 400 mg orally or IV plus flucytosine	BII
	Fluconazole 800 mg orally or IV plus flucytosine	BIII
	Fluconazole 1200 mg orally or IV	CI
Consolidation therapy Duration of therapy: at least 8 weeks	Fluconazole 400 mg orally or IV once daily*	AI
	Itraconazole 200 mg orally or IV twice daily	CI
Maintenance therapy Duration of therapy: at least 1 year and dependent upon response	Fluconazole 200 mg orally	AI
Non-CNS cryptococcosis focal pulmonary disease and isolated cryptococcal antigenemia Duration of treatment: 12 months	Fluconazole 400 mg orally	BIII
Key: * preferred therapy Abbreviations: CNS – central nervous system; HIV = human immunodeficiency virus; IV - intravenous		

IDSA – Practice Guidelines for the Diagnosis and Management of Aspergillosis

A 2016 guideline on the treatment of aspergillosis was performed by the Infectious Disease Society of America (IDSA).⁵ The quality of evidence was graded from low to high and recommendations were issued a “weak” or “strong” designation. There were some conflicts of interest between the IDSA authors and industry; however, the chair was free of conflicts, there is a detailed description of how conflicts are managed and transparent guideline methodology is outlined on the IDSA website. This policy applies to all the IDSA guidelines discussed in this review.

Recommendations for treatment (**Table 3**) and prophylaxis (**Table 4**) for aspergillosis are described below. Duration of treatment is indication dependent. Secondary prophylaxis is recommended for patients who have been treated for aspergillosis who require additional immunosuppression to prevent recurrence. In cases where salvage therapy is indicated, it is recommended to change the antifungal, taper or reverse the immunosuppressant if feasible, and resect any necrotic lesions. Combination antifungal therapy from different classes may be indicated for use as salvage therapy (weak recommendation; moderate-quality of

evidence). Antifungals used in salvage therapy include the following: lipid formulation of amphotericin B, micafungin, caspofungin, posaconazole or itraconazole (strong recommendation; moderate-quality of evidence).

Table 3. IDSA Treatment Recommendations for Aspergillosis⁵

Therapy	Recommendation	Strength of Recommendation	Quality of Evidence
General Treatment Recommendations			
Amphotericin B deoxycholate and lipid derivatives	Initial and salvage therapy when voriconazole is not an option	Strong	moderate
Aerosolized formulations of Amphotericin B	Prophylaxis in patients with prolonged neutropenia	Weak	low
Echinocandins	Salvage therapy alone or in combination, not as primary monotherapy	Strong	moderate
Triazoles	Preferred for treatment and prevention of invasive aspergillosis	Strong	high
	Therapeutic drug monitoring is recommended for patients on prolonged therapy with anticipated drug interactions taking itraconazole, voriconazole, and posaconazole suspension	Strong	moderate
	Trough drug concentration should be obtained for itraconazole, voriconazole, posaconazole and possibly isavuconazole for maximum efficacy and avoidance of toxicities	Strong	moderate
Invasive Pulmonary Aspergillosis (IPA)			
Voriconazole	Recommended as primary treatment for IPA	Strong	high
Liposomal amphotericin B and isavuconazole	Recommended alternative treatments for IPA	Strong	moderate
Other lipid formulations of amphotericin B	Alternative treatment for IPA	Weak	moderate
Combination therapy with voriconazole and echinocandin	Can be considered in select patients	Weak	moderate
Echinocandins	Not recommended as primary therapy	Strong	moderate
Tracheobronchial Aspergillosis (TBA)			
Mold-active triazole or IV lipid formulations of Amphotericin B	Recommended for invasive forms of TBA	Strong	moderate
Central Nervous System Aspergillosis			
Voriconazole	Recommended as primary therapy	Strong	moderate
Lipid Amphotericin B	Recommended for those intolerant or refractory to voriconazole	Strong	moderate
Extrapulmonary Aspergillosis			
Voriconazole	Recommended for central nervous system aspergillosis, aspergillus osteomyelitis and septic arthritis	Strong	moderate
Lipid formulations of amphotericin B	Recommended for those intolerant or refractory to voriconazole	Strong	moderate

Voriconazole plus intravitreal voriconazole or intravitreal amphotericin B	Recommended for aspergillus endophthalmitis	Strong	low
Voriconazole or lipid formulation of amphotericin B	Recommended for aspergillosis of paranasal sinuses	Strong	moderate
Voriconazole or lipid formulation of amphotericin B	Recommended for initial therapy of aspergillus endocarditis, pericarditis and myocarditis	Strong	low
Voriconazole	Recommended for cutaneous aspergillosis, aspergillus peritonitis, or aspergillus ear infection	Strong	low
Voriconazole	Recommended for esophageal, gastrointestinal and hepatic aspergillosis	Weak	low
Amphotericin B deoxycholate	Recommended for renal aspergillosis	Weak	low
Itraconazole or voriconazole	Recommended for aspergillus bronchitis in non-transplant patients	Weak	low
Allergic Syndromes of Aspergillus			
Itraconazole	Recommended for patients with cystic fibrosis who have frequent exacerbations and/or falling FEV1 and monitoring of drug levels	Weak	low
Pediatric Patients with Aspergillosis diagnosis			
Same as adult patients; however, dosing may be different and majority of pharmacokinetic data and experience has been obtained with voriconazole		Strong	high

Table 4. IDSA Prophylaxis Recommendations for Aspergillosis⁵

Therapy	Recommended Indications	Strength of Recommendation	Level of Evidence
Posaconazole	<ul style="list-style-type: none"> prolonged neutropenia with high risk of invasive aspergillosis allogenic HSCT recipients with GVHD who are at high risk for invasive aspergillosis 	Strong	high
Voriconazole	<ul style="list-style-type: none"> prolonged neutropenia with high risk of invasive aspergillosis allogenic HSCT recipients with GVHD who are at high risk for invasive aspergillosis 	Strong	moderate
Micafungin	<ul style="list-style-type: none"> prolonged neutropenia with high risk of invasive aspergillosis 	Weak	low
Caspofungin	<ul style="list-style-type: none"> prolonged neutropenia with high risk of invasive aspergillosis 	Weak	low
Itraconazole	<ul style="list-style-type: none"> prolonged neutropenia with high risk of invasive aspergillosis allogenic HSCT recipients with GVHD who are at high risk for invasive aspergillosis may be limited by absorption and tolerance 	Strong	moderate
Voriconazole, itraconazole or inhaled amphotericin B	<ul style="list-style-type: none"> prophylaxis in patients with lung transplant 	Strong	moderate
Lipid formulation of amphotericin B or echinocandin	<ul style="list-style-type: none"> prolonged neutropenia who remain febrile despite broad-spectrum antibiotic therapy 	Strong	high
Voriconazole	<ul style="list-style-type: none"> prolonged neutropenia who remain febrile despite broad-spectrum antibiotic therapy 	Strong	moderate
Oral itraconazole and voriconazole	<ul style="list-style-type: none"> chronic or saprophytic syndromes of aspergillosis 	Strong	high

Posaconazole	• chronic or saprophytic syndromes of aspergillosis as a third-line therapy	Strong	moderate
Abbreviations: GVHD – graft- versus- host disease; HSCT = hematopoietic stem cell transplant			

IDSA – Clinical Practice Guideline for the Treatment of Coccidioidomycosis

An update to the guidance on the treatment of coccidioidomycosis was complete by IDSA in 2016.⁶ While coccidioidomycosis is not commonly seen in the Pacific Northwest, cases have been reported. Severity of infection can range from pulmonary infections that resolve without treatment to potentially severe pulmonary and extrapulmonary infections. The guideline rates quality of evidence from low to high and recommendations were issued a “weak” or “strong” designation. Guidance for treatment is outline in **Table 5**.⁶ In conclusion, antifungal therapy, especially azole antifungals, are the standard first-line therapy for patients with coccidioidomycosis.

Table 5. IDSA Treatment Recommendations for Coccidioidomycosis⁶

Indication	Recommendation	Strength of Recommendation	Quality of Evidence
Newly diagnosed, uncomplicated coccidioidal pneumonia (non-pregnant adults)	Azole antifungal (e.g., fluconazole greater than or equal to 400 mg)	Strong	low
Symptomatic chronic cavitary coccidioidal pneumonia	Oral fluconazole or itraconazole	Strong	moderate
Rupture coccidioidal cavity	Oral azole therapy or amphotericin B for those you cannot tolerate azoles	Strong	very low
Extrapulmonary soft tissue coccidioidomycosis (not associated with bone)	Azole therapy, fluconazole or itraconazole	Strong	moderate
Bone and/or joint coccidioidomycosis	Azole therapy and amphotericin B for severe osseous disease	Strong	low
Newly diagnosed coccidioidomycosis meningitis	Fluconazole 400-1200 mg daily orally Treatment should be life-long Higher doses of therapy or intrathecal amphotericin B can be given if initial treatment fails	Strong	moderate
Allogenic or autologous hematopoietic or solid organ transplant recipients with active coccidioidomycosis	Fluconazole 400 mg daily or appropriate dose based on renal function	Strong	low
Allogenic or autologous hematopoietic or solid organ transplant recipients with active coccidioidomycosis with very severe and/or rapidly progressing acute pulmonary or disseminated coccidioidomycosis	Amphotericin B followed by fluconazole once patient is stabilized	Strong	low
Recipients of biological response modifiers with active coccidioidomycosis	Oral azole antifungals or amphotericin B if severe	Strong	low
Pregnant women with nonmeningeal coccidioidal infection in first trimester	Intravenous amphotericin B	Strong	moderate
Pregnant women with coccidioidal meningitis	Intrathecal amphotericin B	Strong	moderate

Pregnant women with coccidioidal meningitis after first trimester	Azole antifungal, fluconazole or itraconazole	Strong	low
Infants with suspected coccidioidomycosis	Empiric fluconazole 6-12 mg/kg daily	Strong	low
Patients infected with HIV with clinical evidence of coccidioidomycosis and peripheral blood CD4+ t-lymphocyte count of <250 cells/microliter	Antifungal therapy	Strong	low
Organ transplant recipients without active coccidioidomycosis in endemic areas	Oral azole (e.g., fluconazole 200 mg) for 6-12 months	Strong	low

IDSA – Management of Candidiasis

In 2016, IDSA updated the recommendations for managing candidiasis.⁸ This guideline updates the previous guidance of 2009. The guideline rates quality of evidence from very low to high and recommendations were issued a “weak” or “strong” designation. Treatment recommendations with moderate to high level of evidence (unless only low quality evidence is available) are provided in **Table 6**.⁸ Duration of therapy is dependent upon the diagnosis. Echinocandins are recommended first-line for most episodes of candidemia and invasive candidiasis with the exception of central nervous system, eye and urinary tract infections. The azole antifungals are also commonly indicated first-line and as step-down therapy for candidiasis.

Table 6. IDSA Treatment Recommendations for Candidiasis⁸

Recommendation	First-line Therapy	Alternate Therapies	Strength of Recommendation	Quality of Evidence
Treatment of candidemia in non-neutropenic patients†	<ul style="list-style-type: none"> Echinocandins 	<ul style="list-style-type: none"> fluconazole Amphotericin B is an alternative if there is intolerance, limited availability or resistance 	Strong	high
		<ul style="list-style-type: none"> Transition to from echinocandin fluconazole within 5-7 days 	Strong	moderate
		<ul style="list-style-type: none"> Transition from amphotericin B to fluconazole is recommended within 5-7 days 	Strong	high
Treatment of candidemia in neutropenic patients (including treatment in urinary tract infections)	<ul style="list-style-type: none"> Echinocandin therapy as initial therapy 	<ul style="list-style-type: none"> Lipid formulation of amphotericin B 	Strong	moderate
Neonatal disseminated candidiasis	<ul style="list-style-type: none"> Amphotericin B deoxycholate 	<ul style="list-style-type: none"> Fluconazole 	Strong	moderate
Treatment of intra-abdominal candidiasis	<ul style="list-style-type: none"> Lipid formulation of amphotericin B if there is an intolerance to other antifungals 		Strong	moderate
Valve endocarditis candidiasis	<ul style="list-style-type: none"> Lipid formulation of amphotericin B (with or without flucytosine) high dose echinocandins 	<ul style="list-style-type: none"> Step-down therapy with fluconazole 400-800 mg 	Strong	low

Valve endocarditis candidiasis without valve replacement option and prosthetic valve endocarditis	<ul style="list-style-type: none"> Fluconazole 400-800 mg daily 		Strong	low
Implantable cardiac devices infected with candida	<ul style="list-style-type: none"> Fluconazole 400-800 mg daily 		Strong	low
Candida suppurative thrombophlebitis	<ul style="list-style-type: none"> Lipid formulation of amphotericin B fluconazole 400-800 mg daily echinocandins 	<ul style="list-style-type: none"> Fluconazole step-down therapy 400-800 mg 	Strong	low
Candida osteoarticular infections	<ul style="list-style-type: none"> Fluconazole 400 mg for 6-12 months Echinocandin for at least 2 weeks followed by fluconazole 400 mg for 6-12 months 		Strong	low
Candida septic arthritis	<ul style="list-style-type: none"> Fluconazole 400 mg daily for 6 weeks Echinocandin for 2 weeks followed by fluconazole 400 mg for at least 4 weeks 		Strong	low
Candida <i>Chorioretinitis</i> without vitritis	<ul style="list-style-type: none"> Fluconazole 800 mg loading dose and then 400-800 mg daily Voriconazole 400 mg IV twice daily for 2 doses and then 300 mg daily 	<ul style="list-style-type: none"> Liposomal amphotericin B as an alternative 	Strong	low
CNS candidiasis	<ul style="list-style-type: none"> Liposomal amphotericin B (with or without flucytosine) 	<ul style="list-style-type: none"> Step-down therapy with fluconazole 400-800 mg 	Strong	low
Prophylaxis for patients undergoing urologic procedures	<ul style="list-style-type: none"> Fluconazole 400 mg or amphotericin B deoxycholate for several days before and after procedure 		Strong	low
Symptomatic candida cystitis	<ul style="list-style-type: none"> Fluconazole 200 mg daily for 2 weeks 		Strong	moderate
Symptomatic ascending candida pyelonephritis	<ul style="list-style-type: none"> Fluconazole 200-400 mg daily for 2 weeks 	<ul style="list-style-type: none"> Amphotericin B for fluconazole-resistant organisms 	Strong	low
Vulvovaginal candidiasis	<ul style="list-style-type: none"> Fluconazole 150 mg single dose for uncomplicated and 2-3 doses for severe infection 	<ul style="list-style-type: none"> Recurring infection should be treated with 10-14 days of topical therapy or oral fluconazole followed by oral fluconazole 150 mg weekly for 6 months 	Strong	high

Oropharyngeal candidiasis	<ul style="list-style-type: none"> • Clotrimazole troches 10 mg, 5 times daily • Miconazole mucoadhesive buccal 50 mg tablets 		Strong	high
		• Nystatin suspension as an alternative	Strong	moderate
		• Fluconazole 100-200 mg once daily for 7-14 days for moderate to severe disease	Strong	high
		• Itraconazole, voriconazole, posaconazole or amphotericin B deoxycholate for fluconazole refractory disease	Strong	moderate
		• Echinocandin or amphotericin B deoxycholate for refractory disease	Weak	moderate
		• Fluconazole 100 mg three times weekly for recurrent infections	Strong	high
Esophageal candidiasis	<ul style="list-style-type: none"> • Fluconazole 200-400 mg for 14-21 days 	<ul style="list-style-type: none"> • Itraconazole or voriconazole • IV fluconazole or echinocandins if oral therapy not tolerated • Echinocandin for refractory disease • Fluconazole 100-200 mg three times a week for recurrent esophagitis 	Strong	high
		<ul style="list-style-type: none"> • Amphotericin deoxycholate if oral therapy not tolerated 	Strong	moderate
<p>Key: † Voriconazole is effective for candidemia but does not offer an advantage over fluconazole therapy Abbreviations: CNS- central nervous system; IV – intravenous;</p>				

NCCN – Prevention and Treatment of Cancer-Related Infections, Version 2.2016, NCCN Clinical Practice Guideline

The National Comprehensive Cancer Network (NCCN) 2016 updated guidance on treating cancer-related infections focused on antiviral and antifungal prophylaxis.⁷ Literature was systematically reviewed and recommendations were graded based on **Table 7**. Recommendations as they pertain to antifungal treatment will be presented. Patients at intermediate to high risk of infection should be considered candidates for prophylaxis during neutropenia and for anticipated mucositis (**Table 8**).⁷ Limitations to the guidance include lack of high-quality evidence available for over half of the recommendations.

Table 7. National Comprehensive Cancer Network Categories of Evidence and Consensus⁷

Category	Description
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Table 8. National Comprehensive Cancer Network Recommendations for Antifungal Therapy in Patients with Cancer-related Infections⁷

Disease/Therapy Examples	Antifungal Prophylaxis	Duration	Evidence Grade
Intermediate to High Infection Risk			
ALL	Fluconazole or Micafungin Amphotericin B	Until resolution of neutropenia	Category 2B
MDS (neutropenic) AML (neutropenic)	Posaconazole	Until resolution of neutropenia	Category 1
	Voriconazole, Fluconazole, Micafungin, or Amphotericin B products	Until resolution of neutropenia	Category 2B
Autologous HCT with mucositis	Fluconazole or Micafungin	Until resolution of neutropenia	Category 1
Autologous HCT without mucositis	Consider no prophylaxis	Until resolution of neutropenia	Category 2B
Allogeneic HCT (neutropenic)	Fluconazole or Micafungin	Continue during neutropenia and for at least 75 d after transplant	Category 1
	Voriconazole, Posaconazole, or Amphotericin B products	Continue during neutropenia and for at least 75 d after transplant	Category 2B
Significant GVHD	Posaconazole	Until resolution of significant GVHD	Category 1
	Voriconazole, Echinocandin, Amphotericin B products	Until resolution of significant GVHD	Category 2B
KEY: ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, MDS = myelodysplastic syndromes, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplant			

After review, six guidelines were excluded due to poor quality.^{5,6,10,13-15}

New Indications:

Naftifine 1% and 2% cream (Naftin): In 2016, the FDA approved the use of naftifine in pediatric patients 12 and older with interdigital tinea pedis and tinea cruris and age 2 and above with tinea corporis.¹⁶

Luliconazole 1% cream (Luzu™): An expanded indication was approved by the FDA in 2018 for the use pediatrics ages 2 to under 18 years with tinea corporis.¹⁷ Approval was based on a double-blind, vehicle controlled, multi-center, randomized controlled trial of 75 pediatric patients with a diagnosis of tinea corporis. Clinical cure rates with luliconazole were experienced in 36 patients (71%) compared to 5 (36%) of patients using vehicle cream.¹⁷

Voriconazole (Vfend®): An expanded indication to include patients 2 years and older was approved in 2019 by the FDA.¹⁸ The expanded indication was based on two prospective, open-label, non-comparative, multicenter clinical studies in 53 pediatric patients ages 2 years old to 18 years old who received intravenous voriconazole with an option to switch to oral therapy after day 7 in the first study and after day 5 in the second study. The first study included pediatric patients (n=14 available for mITT analysis) with invasive aspergillosis which demonstrated a successful global response at 6 weeks, defined as a resolution or improvement in clinical signs and symptoms and at least 50% resolution of radiological lesions, in 9 (64%) patients receiving voriconazole. The second study included pediatric patients (n=10 available for mITT analysis) with invasive candidiasis including candidemia and esophageal candidiasis requiring primary or salvage therapy.¹⁸ Success was obtained in 7 (70%) of patients taking voriconazole.¹⁸

New FDA Safety Alerts:

Table 9. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Itraconazole ¹⁹	Sporanox®	10/2017	Precautions	Increased risk of drug interactions due to the ability of itraconazole to inhibit breast cancer resistance protein (BCRP) in addition to already known metabolic pathways
Itraconazole ¹⁹	Sporanox®	05/2018	Precautions	With use of itraconazole in immunocompromised patients (e.g., neutropenia, AIDS or organ transplant patients), the oral bioavailability may be reduced and dose may be to adjusted based on clinical response
Econazole Nitrate ²⁰	Spectazole	06/2018	Warnings and Precautions	May increase anticoagulant effect; monitoring International Normalized Ratio (INR) is recommended
Terbinafine ²¹	Lamisil	01/2019	Warnings and Precautions	Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome
Ketoconazole ²²	Nizoral	05/2019	Safety Communication	FDA warning to limit prescribing of ketoconazole for skin and nail infections due to the risk of serious liver damage, adrenal gland problems and harmful interactions with other medication.

Randomized Controlled Trials:

A total of 166 citations were manually reviewed from the initial literature search. After further review, 165 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 10. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Maertens, et al ³ Phase 3, NI, MC, DB, CG, RCT	Isavuconazole 372 mg (prodrug equivalent to 200 mg isavuconazole)* Vs. Voriconazole† * Given IV three times daily on days one and two and then daily orally or IV thereafter † 6 mg/kg IV twice daily on day 1, 4 mg/kg IV twice daily on day 2, then IV 4 mg/kg twice daily or orally 200 mg twice daily from day 3 onward	Patients with suspected invasive mold disease n=527	All-cause mortality from first dose of study drug till day 42	Isavuconazole: 48 (19%) Voriconazole: 52 (20%) Adjusted TD: -1% (95% CI, -7.8 to 5.7) <i>Isavuconazole was noninferior to voriconazole (NI margin was set at 10%)</i>

Abbreviations: CG = comparative group; DB= double-blind; IV = intravenous; MC = multi-center; NI = non-inferiority; PC = placebo-controlled; PG = parallel group; RCT = randomized clinical trial; TD = treatment difference

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Appendix 1: Current Preferred Drug List**Antifungals, Oral**

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>Route</u>	<u>PDL</u>
clotrimazole	CLOTRIMAZOLE	TROCHE	MUCOUS MEM	Y
fluconazole	DIFLUCAN	SUSP RECON	ORAL	Y
fluconazole	FLUCONAZOLE	SUSP RECON	ORAL	Y
fluconazole	DIFLUCAN	TABLET	ORAL	Y
fluconazole	FLUCONAZOLE	TABLET	ORAL	Y
nystatin	MYCOSTATIN	ORAL SUSP	ORAL	Y
nystatin	NYSTATIN	ORAL SUSP	ORAL	Y
nystatin	NYSTATIN	TABLET	ORAL	Y
flucytosine	ANCOBON	CAPSULE	ORAL	N
flucytosine	FLUCYTOSINE	CAPSULE	ORAL	N
griseofulvin ultramicrosize	GRISEOFULVIN ULTRAMICROSIZE	TABLET	ORAL	N
griseofulvin ultramicrosize	GRIS-PEG	TABLET	ORAL	N
griseofulvin, microsize	GRISEOFULVIN	ORAL SUSP	ORAL	N
griseofulvin, microsize	GRISEOFULVIN	TABLET	ORAL	N
isavuconazonium sulfate	CRESEMBA	CAPSULE	ORAL	N
itraconazole	TOLSURA	CAP SD DSP	ORAL	N
itraconazole	ITRACONAZOLE	CAPSULE	ORAL	N
itraconazole	SPORANOX	CAPSULE	ORAL	N
itraconazole	ITRACONAZOLE	SOLUTION	ORAL	N
itraconazole	SPORANOX	SOLUTION	ORAL	N
itraconazole	ONMEL	TABLET	ORAL	N
ketoconazole	KETOCONAZOLE	TABLET	ORAL	N
miconazole	ORAVIG	MA BUC TAB	BUCCAL	N
nystatin	NYSTATIN	POWDER	ORAL	N
nystatin	NYSTATIN	POWDER(EA)	ORAL	N
posaconazole	NOXAFIL	ORAL SUSP	ORAL	N
posaconazole	NOXAFIL	TABLET DR	ORAL	N
terbinafine HCl	TERBINAFINE HCL	TABLET	ORAL	N
voriconazole	VFEND	SUSP RECON	ORAL	N
voriconazole	VORICONAZOLE	SUSP RECON	ORAL	N
voriconazole	VFEND	TABLET	ORAL	N
voriconazole	VORICONAZOLE	TABLET	ORAL	N

Antifungals, Topical

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>PDL</u>
miconazole nitrate	ANTIFUNGAL CREAM	CREAM (G)	Y
miconazole nitrate	INZO ANTIFUNGAL	CREAM (G)	Y
miconazole nitrate	MICONAZOLE NITRATE	CREAM (G)	Y
nystatin	NYSTATIN	CREAM (G)	Y
nystatin	NYSTATIN	OINT. (G)	Y
acetic ac/resorcino/salicyl ac	ANTIFUNGAL NAIL	TINCTURE	N
butenafine HCl	BUTENAFINE HCL	CREAM (G)	N
butenafine HCl	MENTAX	CREAM (G)	N
ciclopirox	CICLOPIROX	GEL (GRAM)	N
ciclopirox	CICLOPIROX	SHAMPOO	N
ciclopirox	LOPROX	SHAMPOO	N
ciclopirox	CICLODAN	SOLUTION	N
ciclopirox	CICLOPIROX	SOLUTION	N
ciclopirox	PENLAC	SOLUTION	N
ciclopirox olamine	CICLODAN	CREAM (G)	N
ciclopirox olamine	CICLOPIROX	CREAM (G)	N
ciclopirox olamine	LOPROX	CREAM (G)	N
ciclopirox olamine	CICLOPIROX	SUSPENSION	N
ciclopirox olamine	LOPROX	SUSPENSION	N
ciclopirox/skin cleanser no.28	CICLODAN	COMBO. PKG	N
ciclopirox/skin cleanser no.40	LOPROX	COMBO. PKG	N
ciclopirox/skin cleanser no.40	LOPROX	KIT SS-CLN	N
ciclopirox/urea/camph/men/euc	CICLODAN	SOLUTION	N
ciclopirox/urea/camph/men/euc	CICLOPIROX	SOLUTION	N
clotrimazole	ANTIFUNGAL	CREAM (G)	N
clotrimazole	CLOTRIMAZOLE	CREAM (G)	N
clotrimazole	DESENEX	CREAM (G)	N
clotrimazole	FUNGOID	CREAM (G)	N
clotrimazole	LOTRIMIN AF	CREAM (G)	N
clotrimazole	ALEVAZOL	OINT. (G)	N
clotrimazole	CLOTRIMAZOLE	SOLUTION	N
clotrimazole	FUNGOID	SOLUTION	N
clotrimazole/betameth dip/zinc	DERMACINRX THERAZOLE PAK	COMBO. PKG	N
clotrimazole/betamethasone dip	CLOTRIMAZOLE-BETAMETHASONE	CREAM (G)	N
clotrimazole/betamethasone dip	LOTRISONE	CREAM (G)	N
clotrimazole/betamethasone dip	CLOTRIMAZOLE-BETAMETHASONE	LOTION	N
econazole nitrate	ECONAZOLE NITRATE	CREAM (G)	N
econazole nitrate	ECOZA	FOAM	N

efinaconazole	JUBLIA	SOL W/APPL	N
ketoconazole	KETOCONAZOLE	CREAM (G)	N
ketoconazole	EXTINA	FOAM	N
ketoconazole	KETOCONAZOLE	FOAM	N
ketoconazole	KETOCONAZOLE	SHAMPOO	N
ketoconazole	NIZORAL	SHAMPOO	N
luliconazole	LULICONAZOLE	CREAM (G)	N
luliconazole	LUZU	CREAM (G)	N
miconazole nitrate	ATHLETE'S FOOT SPRAY	AERO POWD	N
miconazole nitrate	REMEDY ANTIFUNGAL	CREAM(ML)	N
miconazole nitrate	FUNGOID TINCTURE	KIT	N
miconazole nitrate	ALOE VESTA	OINT. (G)	N
miconazole nitrate	REMEDY PHYTOPLEX ANTIFUNGAL	OINT. (G)	N
miconazole nitrate	ALOE VESTA	OINT.(ML)	N
miconazole nitrate	ANTIFUNGAL POWDER	POWDER	N
miconazole nitrate	DESENEX	POWDER	N
miconazole nitrate	MICONAZORB AF	POWDER	N
miconazole nitrate	REMEDY PHYTOPLEX ANTIFUNGAL	POWDER	N
miconazole nitrate	ZEASORB	POWDER	N
miconazole nitrate	ZEASORB AF	POWDER	N
miconazole nitrate	FUNGOID TINCTURE	TINCTURE	N
miconazole nitrate/zinc ox/pet	MICONAZOLE-ZINC OXIDE-PETROLTM	OINT. (G)	N
miconazole nitrate/zinc ox/pet	VUSION	OINT. (G)	N
naftifine HCl	NAFTIFINE HCL	CREAM (G)	N
naftifine HCl	NAFTIN	CREAM (G)	N
naftifine HCl	NAFTIFINE HCL	GEL (GRAM)	N
naftifine HCl	NAFTIN	GEL (GRAM)	N
nystatin	NYAMYC	POWDER	N
nystatin	NYATA	POWDER	N
nystatin	NYSTATIN	POWDER	N
nystatin	NYSTOP	POWDER	N
nystatin/emollient combo no.54	PEDIADERM AF	CREAM (G)	N
nystatin/emollient combo no.88	NYATA	CMB GEL PD	N
nystatin/triamcin	MYCONEL	CREAM (G)	N
nystatin/triamcin	MYTREX	CREAM (G)	N
nystatin/triamcin	N.T.A.	CREAM (G)	N
nystatin/triamcin	NYSTATIN W/TRIAMCINOLONE	CREAM (G)	N
nystatin/triamcin	NYSTATIN-TRIAMCINOLONE	CREAM (G)	N
nystatin/triamcin	MYTREX	OINT. (G)	N
nystatin/triamcin	N.T.A.	OINT. (G)	N

nystatin/triamcin	NYSTATIN-TRIAMCINOLONE	OINT. (G)	N
oxiconazole nitrate	OXICONAZOLE NITRATE	CREAM (G)	N
oxiconazole nitrate	OXISTAT	CREAM (G)	N
oxiconazole nitrate	OXISTAT	LOTION	N
sertaconazole nitrate	ERTACZO	CREAM (G)	N
sulconazole nitrate	EXELDERM	CREAM (G)	N
sulconazole nitrate	EXELDERM	SOLUTION	N
tavaborole	KERYDIN	SOL W/APPL	N
terbinafine	LAMISIL AT	GEL (GRAM)	N
terbinafine HCl	ATHLETE'S FOOT	CREAM (G)	N
terbinafine HCl	ATHLETE'S FOOT AF	CREAM (G)	N
terbinafine HCl	LAMISIL AT	CREAM (G)	N
terbinafine HCl	TERBINAFINE	CREAM (G)	N
terbinafine HCl	LAMISIL	SPRAY	N
tolnaftate	ATHLETE'S FOOT	AERO POWD	N
tolnaftate	JOCK ITCH	AERO POWD	N
tolnaftate	LAMISIL AF	AERO POWD	N
tolnaftate	TOLNAFTATE	AERO POWD	N
tolnaftate	ANTIFUNGAL CREAM	CREAM (G)	N
tolnaftate	FUNGOID-D	CREAM (G)	N
tolnaftate	TOLNAFTATE	CREAM (G)	N
tolnaftate	ANTI-FUNGAL	POWDER	N
tolnaftate	LAMISIL AF	POWDER	N
tolnaftate	TOLNAFTATE	POWDER	N
tolnaftate	ATHLETE'S FOOT	SPRAY	N
undecylenic ac/zinc undecylena	ANTIFUNGAL CREAM	CREAM (G)	N
undecylenic ac/zinc undecylena	UNDEX-25	OINT. (G)	N
gentian violet	GENTIAN VIOLET	SOLUTION	
gentian violet/brgreen/proflav	TRIPLE DYE	MED. SWAB	
gentian violet/brilliant green	TRIPLE DYE	LIQUID	

Appendix 2: Abstracts of Comparative Clinical Trials

Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial.

Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, Bow EJ, Rahav G, Neofytos D, Aoun M, Baddley JW, Giladi M, Heinz WJ, Herbrecht R, Hope W, Karthaus M, Lee DG, Lortholary O, Morrison VA, Oren I, Selleslag D, Shoham S, Thompson GR 3rd, Lee M, Maher RM, Schmitt-Hoffmann AH, Zeiher B, Ullmann AJ.

BACKGROUND:

Isavuconazole is a novel triazole with broad-spectrum antifungal activity. The SECURE trial assessed efficacy and safety of isavuconazole versus voriconazole in patients with invasive mould disease.

METHODS:

This was a phase 3, double-blind, global multicentre, comparative-group study. Patients with suspected invasive mould disease were randomised in a 1:1 ratio using an interactive voice-web response system, stratified by geographical region, allogeneic haemopoietic stem cell transplantation, and active malignant disease at baseline, to receive isavuconazonium sulfate 372 mg (prodrug; equivalent to 200 mg isavuconazole; intravenously three times a day on days 1 and 2, then either intravenously or orally once daily) or voriconazole (6 mg/kg intravenously twice daily on day 1, 4 mg/kg intravenously twice daily on day 2, then intravenously 4 mg/kg twice daily or orally 200 mg twice daily from day 3 onwards). We tested non-inferiority of the primary efficacy endpoint of all-cause mortality from first dose of study drug to day 42 in patients who received at least one dose of the study drug (intention-to-treat [ITT] population) using a 10% non-inferiority margin. Safety was assessed in patients who received the first dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00412893.

FINDINGS:

527 adult patients were randomly assigned (258 received study medication per group) between March 7, 2007, and March 28, 2013. All-cause mortality from first dose of study drug to day 42 for the ITT population was 19% with isavuconazole (48 patients) and 20% with voriconazole (52 patients), with an adjusted treatment difference of -1.0% (95% CI -7.8 to 5.7). Because the upper bound of the 95% CI (5.7%) did not exceed 10%, non-inferiority was shown. Most patients (247 [96%] receiving isavuconazole and 255 [98%] receiving voriconazole) had treatment-emergent adverse events ($p=0.122$); the most common were gastrointestinal disorders (174 [68%] vs 180 [69%]) and infections and infestations (152 [59%] vs 158 [61%]). Proportions of patients with treatment-emergent adverse events by system organ class were similar overall. However, isavuconazole-treated patients had a lower frequency of hepatobiliary disorders (23 [9%] vs 42 [16%]; $p=0.016$), eye disorders (39 [15%] vs 69 [27%]; $p=0.002$), and skin or subcutaneous tissue disorders (86 [33%] vs 110 [42%]; $p=0.037$). Drug-related adverse events were reported in 109 (42%) patients receiving isavuconazole and 155 (60%) receiving voriconazole ($p<0.001$).

INTERPRETATION:

Isavuconazole was non-inferior to voriconazole for the primary treatment of suspected invasive mould disease. Isavuconazole was well tolerated compared with voriconazole, with fewer study-drug-related adverse events. Our results support the use of isavuconazole for the primary treatment of patients with invasive mould disease.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to July Week 3 2019

Search Strategy:

#	Searches	Results
1	clotrimazole.mp. or Clotrimazole/	2714
2	fluconazole.mp. or Fluconazole/	11797
3	nystatin.mp. or Nystatin/	4873
4	flucytosine.mp. or Flucytosine/	3473
5	griseofulvin.mp. or Griseofulvin/	3690
6	isavuconazonium.mp.	40
7	itraconazole.mp. or Itraconazole/	8840
8	ketoconazole.mp. or Ketoconazole/	8523
9	miconazole.mp. or Miconazole/	3048
10	posaconazole.mp.	2108
11	terbinafine.mp. or Terbinafine/	2482
12	voriconazole.mp. or Voriconazole/	5368
13	acetic acid.mp. or Acetic Acid/	37476
14	butenafine.mp.	83
15	ciclopirox.mp. or Ciclopirox/	524
16	econazole.mp. or Econazole/	924
17	efinaconazole.mp.	115
18	luliconazole.mp.	68
19	naftifine.mp.	186
20	oxiconazole.mp.	107
21	sertaconazole.mp.	112

22	sulconazole.mp.	81
23	tavaborole.mp.	78
24	tolnaftate.mp. or Tolnaftate/	255
25	gentian violet.mp. or Gentian Violet/	2579
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	83394
27	limit 26 to (english language and humans and yr="2015 -Current")	5752
28	limit 27 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	166

Appendix 4: Key Inclusion Criteria

Population	Patients with a fungal infection diagnosis
Intervention	Topical or oral antifungal treatment
Comparator	Other antifungal agents, placebo, or matched controls
Outcomes	Clinical cure, mycological cure, resolution of symptoms or all-cause mortality
Timing	At onset of infection
Setting	Outpatient and inpatient

Appendix 5: Prior Authorization Criteria

Antifungals

Goal(s):

- Approve use of antifungals only for OHP-funded diagnoses. Minor fungal infections of skin, nails and scalp, such as dermatophytosis and candidiasis, are only funded when complicated by an immunocompromised host.

Length of Authorization:

- See criteria

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at ¹⁷
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: Examples of FUNDED indications (1/1/15)

ICD-10	Description
B373	Candidiasis of vulva and vagina
B371	Candidiasis of the lung
B377	Disseminated Candidiasis
B375-376, B3781-3782, B3784-3789	Candidiasis of other specified sites
B380-B384, B3889, B389	Coccidioidomycosis various sites
B392-395, B399, G02, H32, I32, I39, J17	Histoplasmosis
B409, B410, B419, B480	Blastomycosis
B420-427, B429, B439, B449-450, B457, B459, B469, B481-482, B488, B49	Rhinosporidiosis, Sporotrichosis, Chromoblastomycosis, Aspergillosis, Mycotis Mycetomas, Cryptococcosis, Allescheriosis, Zygomycosis, Dematiaceous Fungal Infection, Mycoses Nec and Nos
B488	Mycosis, Opportunistic
B4481	Bronchopulmonary Aspergillus, Allergic
N739-751, N759, N760-N771(except N72)	Inflammatory disease of cervix vagina and vulva

L3019,L3029, L3039, L3049	Cellulitis and abscess of finger and toe
P375	Neonatal Candida infection

Table 2: Examples of NON-FUNDED indications (1/1/15)

ICD-10	Description
L2083, L210-211, L218-219, L303	Erythematous squamous dermatosis
L22	Diaper or napkin rash
L20.0-20.82, L20.84-20.89	Other atopic dermatitis and related conditions
L240-242, L251-255, L578, L579, L230, L2381, L2481, L250, L252, L258-259, L551-552, L568, L589	Contact dermatitis and other eczema
L530-532, L510, L518-519, L52, L710-711, L718, L930, L932, L490-L499, L26, L304, L538, L920, L951, L982, L539	Erythematous conditions
L438,L441-443, L449,L661	Lichen Planus
L700-702, L708	Rosacea or acne
B351	Tinea unguium (onychomycosis)
B360	Pityriasis versicolor
B362	Tinea blanca
B363	Black piedra
B368, B369	Mycoses, superficial
B372	Cutaneous candidiasis
B379	Candidiasis, unspecified
R21	Rash and other nonspecific skin eruption

Table 3: Criteria driven diagnoses (1/1/15)

ICD-10	Description
B350	Dermatophytosis of scalp and beard (tinea capitis/ tinea barbae)
B352	Dermatophytosis of hand (tinea manuum)
B356	Dermatophytosis of groin and perianal area (tinea cruris)
B353	Dermatophytosis of foot (tinea pedis)
B355	Dermatophytosis of body (tinea corporis / tinea imbricate)
B358	Deep seated dermatophytosis
B358-B359	Dermatophytosis of other specified sites - unspecified site

B361	Tinea nigra
B370,B3783	Candidiasis of mouth
B3742,B3749	Candidiasis of other urogenital sites

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis funded by OHP? (See examples in Table 1).	Yes: Go to #3	No: Go to #4
3. Will the prescriber consider a change to a preferred product? Message: <ul style="list-style-type: none"> Preferred products do not require PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety. 	Yes: Inform prescriber of preferred alternatives.	No: Approve for 3 months or course of treatment.
4. Is the prescriber a hematology, oncology or infectious disease specialty prescriber requesting voriconazole?	Yes: Approve for 3 months or course of treatment.	No: Go to #5
5. Is the diagnosis not funded by OHP? (see examples in Table 2).	Yes: Pass to RPh. Deny; not funded by OHP	No: Go to #6
6. Is the diagnosis funded by OHP if criteria are met? (see examples in Table 3).	Yes: Go to #7	No: Go to #9
7. Is the patient immunocompromised (examples below)? <ul style="list-style-type: none"> Does the patient have a current (not history of) diagnosis of cancer AND is currently undergoing 	Yes: Record ICD-10 code. Approve as follows: (immunocompromised patient)	No: Go to #8

<p>Chemotherapy or Radiation? Document therapy and length of treatment. OR</p> <ul style="list-style-type: none"> • Does the patient have a diagnosis of HIV/AIDS? OR • Does the patient have sickle cell anemia? • Poor nutrition, elderly or chronically ill? • Other conditions as determined and documented by a RPh. 	<p>ORAL & TOPICAL</p> <ul style="list-style-type: none"> • Course of treatment. • If length of therapy is unknown, approve for 3 months. 																	
<p>8. Is the patient currently taking an immunosuppressive drug? Document drug.</p> <p>Pass to RPh for evaluation if drug not in list.</p> <p>Immunosuppressive drugs include but are not limited to:</p> <table border="1" data-bbox="159 922 774 1224"> <tr> <td>azathioprine</td> <td>leflunomide</td> </tr> <tr> <td>basiliximab</td> <td>mercaptopurine</td> </tr> <tr> <td>cyclophosphamide</td> <td>methotrexate</td> </tr> <tr> <td>cyclosporine</td> <td>mycophenolate</td> </tr> <tr> <td>etanercept</td> <td>rituximab</td> </tr> <tr> <td>everolimus</td> <td>sirolimus</td> </tr> <tr> <td>hydroxychloroquine</td> <td>tacrolimus</td> </tr> <tr> <td>infliximab</td> <td></td> </tr> </table>	azathioprine	leflunomide	basiliximab	mercaptopurine	cyclophosphamide	methotrexate	cyclosporine	mycophenolate	etanercept	rituximab	everolimus	sirolimus	hydroxychloroquine	tacrolimus	infliximab		<p>Yes: Approve as follows: (immunocompromised patient)</p> <p>ORAL & TOPICAL</p> <ul style="list-style-type: none"> • Course of treatment. • If length of therapy is unknown, approve for 3 months. 	<p>No: Pass to RPh. Deny; not funded by the OHP</p>
azathioprine	leflunomide																	
basiliximab	mercaptopurine																	
cyclophosphamide	methotrexate																	
cyclosporine	mycophenolate																	
etanercept	rituximab																	
everolimus	sirolimus																	
hydroxychloroquine	tacrolimus																	
infliximab																		

9. RPh only: All other indications need to be evaluated to see if it is an OHP-funded diagnosis:

- If funded: may approve for treatment course with PRN renewals. If length of therapy is unknown, approve for 3-month intervals only.
- If not funded: Deny; not funded by the OHP.
 - Deny non-fungal diagnosis (medical appropriateness)
 - Deny fungal ICD-10 codes that do not appear on the OHP list pending a more specific diagnosis code (not funded by the OHP).
 - Forward any fungal ICD-10 codes not found in the Tables 1, 2, or 3 to the Lead Pharmacist. These codes will be forwarded to DMAP to be added to the Tables for future requests.

P&T Review: 11/19 (KS) 7/15 (kk); 09/10; 2/06; 11/05; 9/05; 5/05
Implemented: 5/1/16; 8/15; 1/1/11; 7/1/06; 11/1/0; 9/1/0