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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.[2]
- Evidence for the use of topical antifungals for seborrheic dermatitis was insufficient to draw strong conclusions regarding efficacy or safety.[4]
- 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.[5]
- 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.[6,7,8,9,10]
- 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.
- Evaluate costs in executive session.

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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, allogenic hematopoietic stem cell transplant and acquired immunodeficiencies requiring oral or intravenous antifungal therapy.[7] 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.[11] 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.[12] 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.[13] 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 meningocephalitis, with a limited role in select invasive candidiasis infections. Due to high levels of resistance, flucytosine is not commonly used as monotherapy.[14] 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 a 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.[7]

**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.[2] 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.[2] 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.[2] 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).[2] 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).[4] 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).[4] 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.[6] 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**.[15]

**Table 1. Recommendation Strength and Quality Definitions**[6]

| 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**).[6] 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.[6] If secondary prophylaxis (i.e., maintenance/supressive 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).[6]

**Table 2. Antifungal Treatment Recommendations for Opportunistic Infections in Patients with HIV**[6]

| Indication for Therapy | Recommendation | Strength of Evidence |
|---|---|---|
| **Oropharyngeal Candidiasis**<br>Duration of therapy: 7-14 days | Fluconazole 100 mg tablets or solution once daily* | AI |
| | Miconazole 50 mg mucoadhesive buccal tablets once daily | BI |
| | Clotrimazole troches 10 mg five times a day | BI |
| | Nystatin suspension or pastilles four times daily | BII |
| | Itraconazole 200 mg oral solution daily | BI |
| | Posaconazole 400 mg oral suspension twice daily for one day and then 400 mg daily | BI |
| **Esophageal disease**<br>Duration of therapy: 14-21 days | Fluconazole 100 mg (up to 400 mg) once daily (oral or IV)* | AI |
| | Itraconazole oral solution 200 mg daily* | AI |
| | Oral itraconazole capsules (capsules not recommended due to variable absorption) | CII |
| | Isavuconazole 200 mg orally as a loading dose, followed by 50 mg daily | BI |
| | Isavuconazole 400 mg orally as a loading dose, followed by 100 mg daily | B1 |
| | Isavuconazole 400 mg orally once weekly | BI |
| | Voriconazole 200 mg PO or IV twice daily | BI |
| | Amphotericin B deoxycholate IV daily | BI |
| | Lipid formulation of amphotericin B IV daily | BIII |
| | Echinocandins (caspofungin, micafungin, and anidulafungin) (doses not provided) | BI |
| **Vulvovaginal Candidiasis**<br>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**<br>Duration of therapy: depends on response<br>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* | AI |
| | Fluconazole 400 mg orally once daily | BI |
| 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 |

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| | 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**<br>Induction therapy<br>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<br>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<br>Duration of therapy: at least 1 year and dependent upon response | Fluconazole 200 mg orally | AI |
| Non-CNS cryptococococcosis focal pulmonary disease and isolated cryptococcal antigenemia<br>Duration of treatment: 12 months | Fluconazole 400 mg orally | BIII |
| Key: * preferred therapy<br>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).[7] The quality of evidence was graded from low to high and recommendations were issued a "weak" or "strong" designation. 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 Aspergillosis**[7]

| 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 |

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| 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 Aspergillosis**[7]

| Therapy | Recommended Indications | Strength of Recommendation | Level of Evidence |
|---|---|---|---|
| Posaconazole | • prolonged neutropenia with high risk of invasive aspergillosis<br>• allogenic HSCT recipients with GVHD who are at high risk for invasive aspergillosis | Strong | high |
| Voriconazole | • prolonged neutropenia with high risk of invasive aspergillosis<br>• allogenic HSCT recipients with GVHD who are at high risk for invasive aspergillosis | Strong | moderate |
| Micafungin | • prolonged neutropenia with high risk of invasive aspergillosis | Weak | low |
| Caspofungin | • prolonged neutropenia with high risk of invasive aspergillosis | Weak | low |
| Itraconazole | • prolonged neutropenia with high risk of invasive aspergillosis<br>• allogenic HSCT recipients with GVHD who are at high risk for invasive aspergillosis<br>• may be limited by absorption and tolerance | Strong | moderate |
| Voriconazole, itraconazole or inhaled amphotericin B | • prophylaxis in patients with lung transplant | Strong | moderate |
| Lipid formulation of amphotericin B or echinocandin | • prolonged neutropenia who remain febrile despite broad-spectrum antibiotic therapy | Strong | high |
| Voriconazole | • prolonged neutropenia who remain febrile despite broad-spectrum antibiotic therapy | Strong | moderate |
| Oral itraconazole and voriconazole | • 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.[8] 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**.[8] In conclusion, antifungal therapy, especially azole antifungals, are the standard first-line therapy for patients with coccidioidomycosis.

**Table 5. IDSA Treatment Recommendations for Coccidioidomycosis**[8]

| 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<br>Treatment should be life-long<br>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 |

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| 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.[10] 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**.[10] 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 Candidiasis**[10]

| Recommendation | First-line Therapy | Alternate Therapies | Strength of Recommendation | Quality of Evidence |
|---|---|---|---|---|
| Treatment of candidemia in non-neutropenic patients† | • Echinocandins | • fluconazole<br>• Amphotericin B is an alternative if there is intolerance, limited availability or resistance | Strong | high |
| | | • Transition to from echinocandin fluconazole within 5-7 days | Strong | moderate |
| | | • 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) | • Echinocandin therapy as initial therapy | • Lipid formulation of amphotericin B | Strong | moderate |
| Neonatal disseminated candidiasis | • Amphotericin B deoxycholate | • Fluconazole | Strong | moderate |
| Treatment of intra-abdominal candidiasis | • Lipid formulation of amphotericin B if there is an intolerance to other antifungals | | Strong | moderate |
| Valve endocarditis candidiasis | • Lipid formulation of amphotericin B (with or without flucytosine)<br>• high dose echinocandins | • Step-down therapy with fluconazole 400-800 mg | Strong | low |

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| Valve endocarditis candidiasis without valve replacement option and prosthetic valve endocarditis | • Fluconazole 400-800 mg daily | | Strong | low |
| Implantable cardiac devices infected with candida | • Fluconazole 400-800 mg daily | | Strong | low |
| Candida suppurative thrombophlebitis | • Lipid formulation of amphotericin B<br>• fluconazole 400-800 mg daily<br>• echinocandins | • Fluconazole step-down therapy 400-800 mg | Strong | low |
| Candida osteoarticular infections | • Fluconazole 400 mg for 6-12 months<br>• Echinocandin for at least 2 weeks followed by fluconazole 400 mg for 6-12 months | | Strong | low |
| Candida septic arthritis | • Fluconazole 400 mg daily for 6 weeks<br>• Echinocandin for 2 weeks followed by fluconazole 400 mg for at least 4 weeks | | Strong | low |
| Candida *Chorioretinitis* without vitritis | • Fluconazole 800 mg loading dose and then 400-800 mg daily<br>• Voriconazole 400 mg IV twice daily for 2 doses and then 300 mg daily | • Liposomal amphotericin B as an alternative | Strong | low |
| CNS candidiasis | • Liposomal amphotericin B (with or without flucytosine) | • Step-down therapy with fluconazole 400-800 mg | Strong | low |
| Prophylaxis for patients undergoing urologic procedures | • Fluconazole 400 mg or amphotericin B deoxycholate for several days before and after procedure | | Strong | low |
| Symptomatic candida cystitis | • Fluconazole 200 mg daily for 2 weeks | | Strong | moderate |
| Symptomatic ascending candida pyelonephritis | • Fluconazole 200-400 mg daily for 2 weeks | • Amphotericin B for fluconazole-resistant organisms | Strong | low |
| Vulvovaginal candidiasis | • Fluconazole 150 mg single dose for uncomplicated and 2-3 doses for severe infection | • 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 |

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| Oropharyngeal candidiasis | • Clotrimazole troches 10 mg, 5 times daily<br>• 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 | • Fluconazole 200-400 mg for 14-21 days | • Itraconazole or voriconazole<br>• IV fluconazole or echinocandins if oral therapy not tolerated<br>• Echinocandin for refractory disease<br>• Fluconazole 100-200 mg three times a week for recurrent esophagitis | Strong | high |
| | | • Amphotericin deoxycholate if oral therapy not tolerated | Strong | moderate |
| Key: † Voriconazole is effective for candidemia but does not offer an advantage over fluconazole therapy<br>Abbreviations: CNS- central nervous system; IV – intravenous; | | | | |

*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.[9] 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).**[9] Limitations to the guidance include lack of high-quality evidence available for over half of the recommendations.

**Table 7. NCCN Categories of Evidence and Consensus**[9]

| 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. NCCN Recommendations for Antifungal Therapy in Patients with Cancer-related Infections**[9]

| Disease/Therapy Examples | Antifungal Prophylaxis | Duration | Evidence Grade |
|---|---|---|---|
| **Intermediate to High Infection Risk** | | | |
| ALL | Fluconazole or Micafungin<br>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.[7,8,12,15–17]

**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 coporis.[18]

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.[19] 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.[19]

Voriconazole (Vfend®): An expanded indication to include patients 2 years and older was approved in 2019 by the FDA.[20] 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.[20] Success was obtained in 7 (70%) of patients taking voriconazole.[20]

**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[21] | 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[21] | 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[22] | Spectazole | 06/2018 | Warnings and Precautions | May increase anticoagulant effect; monitoring International Normalized Ratio (INR) is recommended |
| Terbinafine[23] | Lamisil | 01/2019 | Warnings and Precautions | Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome |
| Ketoconazole[24] | 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[5]<br><br>Phase 3, NI, MC, DB, CG, RCT | Isavuconazole 372 mg (prodrug equivalent to 200 mg isavuconazole)*<br><br>Vs.<br><br>Voriconazole†<br><br>* Given IV three times daily on days one and two and then daily orally or IV thereafter<br><br>† 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<br><br>n=527 | All-cause mortality from first dose of study drug till day 42 | Isavuconazole: 48 (19%)<br>Voriconazole: 52 (20%)<br><br>Adjusted TD: -1% (95% CI, -7.8 to 5.7)<br>*Isavuconazole was noninferior to voriconazole (NI margin was set at 10%)* |

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**

| Generic | Brand | Form | Route | PDL |
|---|---|---|---|---|
| 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**

| Generic | Brand | Form | PDL |
|---|---|---|---|
| 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 |

# 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 | Rhinosporidosis, Sporotrichosis, Chromoblastomycosis, Aspergillosis, Mycotis Mycetomas, Cryptococcosis, Allescheriosis, Zygomycosis, Dematiacious 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 | Erythematosquamous 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?<br>Message:<br>• Preferred products do not require PA.<br>• 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)?<br>• 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 |

<table>
<tr>
<td>Chemotherapy or Radiation? Document therapy and length of treatment. OR<br>• Does the patient have a diagnosis of HIV/AIDS? OR<br>• Does the patient have sickle cell anemia?<br>• Poor nutrition, elderly or chronically ill?<br>• Other conditions as determined and documented by a RPh.</td>
<td>ORAL & TOPICAL<br>• Course of treatment.<br>• If length of therapy is unknown, approve for 3 months.</td>
<td></td>
</tr>
<tr>
<td>8. Is the patient currently taking an immunosuppressive drug? Document drug.<br><br>Pass to RPh for evaluation if drug not in list.<br><br>Immunosuppressive drugs include but are not limited to:
<table>
<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>
</td>
<td>Yes: Approve as follows: (immunocompromised patient)<br><br>ORAL & TOPICAL<br>• Course of treatment.<br>• If length of therapy is unknown, approve for 3 months.</td>
<td>No: Pass to RPh. Deny; not funded by the OHP</td>
</tr>
</table>

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*