Antimicrobial Stewardship News

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Treatment of Candidiasis & Antifungal Stewardship Opportunities

Introduction

Candida are yeasts that are abundant in normal human flora of the skin, mouth, and gut. Disease occurs when natural protective barriers or host defenses are compromised, such as in scenarios of mucositis or intravascular catheters. *Candida* infections may occur in all types of practice settings. Clinical presentation may range in severity from asymptomatic colonization to invasive candidiasis with multisystem organ failure.[1] Identifying patients at risk for invasive candidiasis remains challenging, and appropriate management is complex. This newsletter will outline appropriate treatment recommendations as well as antifungal stewardship opportunities for patients with candidiasis.

Infections Caused by *Candida* Species

Infections caused by *Candida* species are classified as invasive (e.g., bloodstream or other deep-seated infections such as osteomyelitis) or non-invasive (e.g., mucosal infections). Many different *Candida* species cause human disease, and some *Candida* species are more resistant to fluconazole than others. For example, the majority of *C. albicans* isolates are susceptible to fluconazole whereas all *C. krusei* isolates exhibit intrinsic fluconazole resistance (**Table 1)**. Due to this range in susceptibilities, *Candida* species must be properly identified and susceptibility tested to appropriately manage invasive candidiasis.

Table 1. Incidence and Susceptibility of Candida Species Causing Human Disease in North America[2]

Organism	Incidence	Fluconazole Susceptibility
C. albicans	46%	+++
C. glabrata	26%	++
C. parapsilosis	16%	+++
C. tropicalis	8%	+++
C. krusei	3%	-

Candiduria

The presence of candiduria usually triggers a physician to consider whether a patient has a *Candida* urinary tract infection (UTI) that requires treatment. In asymptomatic patients, candiduria almost always represents colonization. Removing the indwelling urinary catheter generally eradicates candiduria. A randomized controlled trial evaluating fluconazole vs placebo for 14-days in asymptomatic candiduric patients found that initial eradication rates were higher in patients receiving fluconazole.[3] However, there was no difference between groups in candiduria rates at day 14, which suggests treatment with fluconazole does not result in long-term eradication or clinical benefit. Candiduria should be treated however, in certain high-risk groups, such as neutropenic patients and very low-birth-weight infants (<1500 g). Candiduric patients undergoing urologic manipulation should be treated with fluconazole for several days prior to the procedure.[1]

Treatment for Asymptomatic Candiduria:

All Patients: Remove Urinary Catheter

High Risk Groups: Fluconazole x 14 days

Patients with *Candida* UTIs usually present with symptoms of cystitis or pyelonephritis. *Candida* UTIs can evolve as ascending infections beginning in the lower urinary tract or from hematogenous spread to the kidneys. *Candida albicans* is the most common cause of fungal UTIs and is generally susceptible to fluconazole. In contrast, UTIs caused by fluconazole-resistant *C. glabrata* as well as *C. krusei* can be extremely difficult to treat because the echinocandins and other azole antifungal agents do not achieve adequate urine concentrations. Treatment options and durations for fluconazole-resistant and -susceptible *Candida* UTIs are shown in **Table 2**.

Table 2. Treatment Options for *Candida* UTI[1]

Susceptibility	Agent	Duration
Fluconazole-susceptible	Fluconazole 200-400 mg/day	14 days
Fluconazole-resistant	Amphotericin B (AmB) deoxycholate[a] 0.3-0.6 mg/kg/day	1-7 days
	Flucytosine 25 mg/kg QID	7-10 days
	AmB deoxycholate bladder irrigation, 50 mg/L	5 days

[a] Lipid formulations do not appear to achieve adequate urine concentrations to treat UTIs

Candidemia

Candida species isolated from a blood culture should never be considered a contaminant. Patients should be promptly initiated on systemic antifungal therapy, even when Candida is isolated from a single blood culture. Potential primary sources of the fungemia should be carefully evaluated. The 2015 IDSA guidelines recommended several procedures as part of the workup of candidemic patients (**Table 3**). Stewardship programs implementing a bundled approach to this workup have reported quality improvements for candidemic patients.[4]

Table 3. Checklist for Managing Candidemia[1]

Infectious Workup	▪ Species identification and susceptibility testing
	▪ Repeat cultures every 48 hours until clear
	▪ Search for and evaluate source
	▪ Remove central line
	▪ Perform dilated ophthalmologic exam

Local epidemiology is an important factor to consider when developing empiric treatment guidelines for candidemic patients at your hospital. The echinocandins (eg, micafungin) are recommended by the IDSA as first-line initial therapy. However, at hospitals with low rates of fluconazole-resistant *Candida spp*., fluconazole is an appropriate alternative in non-critically ill, non-neutropenic patients with no recent azole exposure. Patients with candidemia that are treated with oral or intravenous fluconazole should receive a loading dose of 800 mg x 1, followed by 400 mg (or the renally-adjusted equivalent) daily. Oral therapy is appropriate for patients that are tolerating medications by mouth.

***Candida* isolated in blood cultures should NEVER be considered a contaminant.**

For patients initially receiving an echinocandin, stepdown therapy to an oral agent (such as fluconazole or voriconazole (reserve for patients with *C. krusei*)) after 5-7 days is appropriate if the patient is clinically-stable, blood cultures cleared following antifungal initiation, and the isolate is susceptible to the agent. If fluconazole is considered for step-down therapy for infections caused by *C. glabrata*, higher doses (800 mg daily or the renally-adjusted equivalent) are recommended. Treatment duration for candidemia should be at least 14 days beginning on the first day of negative cultures. Complex infections, such as *Candida* endocarditis, should be treated for extended durations.

Candida in the Lower Respiratory Tract

Candida species are commonly isolated from the respiratory tract of patients who are intubated or have a chronic tracheostomy. These organisms do not require treatment, as they almost always represent colonization and not infection. Pneumonia due to *Candida* species is extremely rare, and much of the limited data available are clinical case series from autopsy studies of severely immunocompromised patients.[5] There are no evidence-based diagnostic criteria for *Candida* pneumonia, and many experts believe a firm diagnosis requires histopathological evidence. In patients that are severely immunosuppressed, isolation of *Candida* species from the respiratory tract should trigger a search for evidence of invasive candidiasis. The current IDSA guidelines on the management of invasive candidiasis make no recommendations regarding the treatment of *Candida* pneumonia.[1] Overall, *Candida spp.* isolated from respiratory cultures in most patients represents colonization and therefore should not be treated.

Anti-Fungal Prophylaxis in the ICU

Mortality rates in patients with invasive candidiasis in the ICU remain high; therefore, antifungal prophylaxis has been studied as a means to prevent its occurrence. Use of antifungal prophylaxis with fluconazole remains

controversial because it increases the risk for developing an infection with fluconazole-resistant pathogens. In addition, known risks associated with azoles include drug-induced hepatitis, drug-drug interactions, and QT prolongation. To date, four meta-analyses have evaluated fluconazole prophylaxis in ICU patients.[6-9] Even though all four demonstrated a reduction in invasive candidiasis, only two demonstrated a reduction in candidemia and only one showed a reduction in mortality. Based on the risk of unintended consequences, DASON does NOT recommend routine antifungal prophylaxis in community hospital ICUs. This recommendation is based on our understanding of low, <5%, incidence of invasive candidiasis.[1] Certain patients at very high risk for invasive candidiasis may be considered appropriate candidates for antifungal prophylaxis on a case-by-case basis. Risk factors include central venous catheters, parenteral nutrition, hemodialysis, trauma, broad-spectrum antibiotics, and recent surgery (particularly abdominal surgery). In such patients, fluconazole is an appropriate agent unless there is a high rate of fluconazole-resistant organisms in the unit or facility, in which cases an echinocandin would be preferred.

DASON does NOT recommend routine antifungal prophylaxis in community hospital ICUs

Oropharyngeal & Esophageal Candidiasis

Oropharyngeal and esophageal candidiasis often occur in the setting of immune dysfunction. Patients at risk include those with HIV/AIDS (CD4 count <200), diabetes, malignancy, steroid use, radiation, antibiotic therapy, and dentures. *C. albicans* is the most common pathogen, although infections caused by other *Candida* species have been described. Most cases of oropharyngeal candidiasis respond to topical therapy (**Table 4**). Systemic therapy should be reserved for moderate to severe or refractory disease to reduce the risk for collateral damage.

Table 4. Treatment for Oropharyngeal Candidiasis

Severity	Therapy
Mild	Preferred: ▪ Clotrimazole troches, 10 mg 5 times/day x 7-14 days ▪ Miconazole mucoadhesive buccal 50 mg tablet daily x 7-14 days Alternative: ▪ Nystatin suspension (100,000 U/mL) 4-6 mL 4 times daily, *OR* 1-2 nystatin pastilles (200,000 U each) 4 times daily x 7-14 days
Moderate to Severe	Fluconazole 100-200 mg daily x 7-14 days

In patients presenting with oropharyngeal candidiasis and difficulty or painful swallowing, esophageal candidiasis should be considered. Unlike oropharyngeal disease, esophageal candidiasis should always be treated with systemic antifungal therapy. We outline several factors to consider when selecting systemic therapy below (**Figures 1 & 2**).

Figure 1. Treatment of Esophageal Candidiasis

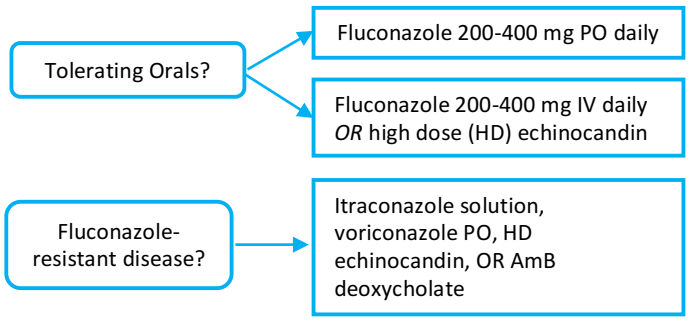
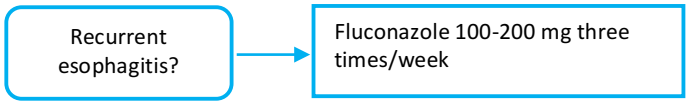


Figure 2. Treatment of Recurrent Esophageal Candidiasis



Appropriate duration for esophageal candidiasis is 14 to 21 days of systemic antifungal therapy. While oral fluconazole is the preferred therapy, patients unable to tolerate oral medications require intravenous therapy. Patients in clinical trials of esophageal candidiasis experienced higher relapse rates when treated with routine doses of echinocandins compared to those treated with fluconazole.[10,11] If fluconazole is not an

option due to pathogen resistance or other patient-specific factors, higher doses of echinocandins should be used. For all patients initiated on intravenous therapy, consider de-escalating to oral therapy when the patient can tolerate oral administration. Lastly, recurrent esophagitis may require chronic suppressive therapy with fluconazole three times weekly until underlying, host-related factors improve. For example, effective antiretroviral therapy decreases the incidence of recurrent infection among patients with HIV/AIDS.

Take Home Message:

- *Candida* species are abundant in normal human flora and cause infection when normal host defenses or mucosal barriers are compromised.
- *Candida* isolated from the urine or respiratory tract often represents colonization, which does not necessarily require antifungal treatment.
- *Candida* isolated from blood culture(s) should never be considered a contaminant. Patients should be treated with anti-fungal therapy promptly and be fully evaluated to identify and control the primary source.
- Local epidemiology should guide empiric treatment selection for candidemic patients.
- DASON recommends against routine anti-fungal prophylaxis in the ICU setting at community hospitals.
- Oropharyngeal candidiasis can be successfully managed with topical therapy. Esophageal candidiasis should be treated with systemic antifungal therapy for 14-21 days.

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