

MANAGEMENT OF CANDIDA INFECTIONS IN SURGICAL PATIENTS

SUMMARY

Candida infections are associated with significant mortality. Patients with microbiologic evidence of candidemia or disseminated candidiasis should receive systemic antifungal therapy. Such therapy should be considered in critically ill patients who have a positive culture for yeast (sputum, urine, wound, fluid) and at least one risk factor for invasive fungal infection. In the non-critically ill, determination of true fungal infection and subsequent therapy should be based upon colony counts, clinical findings, and the presence of risk factors. Empiric antifungal therapy is justified in patients with negative fungal cultures if they have systemic evidence of infection and two or more risk factors for fungal infection. Empiric therapy should also be administered following gastrointestinal perforation in patients with risk factors.

RECOMMENDATIONS

- **Level 1**
 - None
- **Level 2**
 - All patients with candidemia should be treated with a systemic antifungal agent.
 - Central venous and urinary catheters should be changed if they culture positive for yeast.
 - Empiric antifungal therapy should be considered in patients with evidence of systemic infection AND 2 or more risk factors.
 - Persistent candiduria following catheter change or removal should be treated with a systemic antifungal agent.
 - Identification of all *Candida spp.* is required to ensure appropriate antifungal therapy.
 - Surgical debridement and/or drainage of localized fungal infections should be performed where possible.
- **Level 3**
 - Antifungal therapy should be initiated following gastrointestinal perforation in the presence of peritonitis and one or more risk factors.
 - Candiduria in the presence of a structural abnormality or obstruction of the urinary tract or immunosuppression should be treated with a systemic antifungal agent.
 - Central venous catheters should be changed when candidemia is identified.
 - Critically ill patients who have a positive culture for yeast and at least one risk factor should receive a systemic antifungal agent.
 - Patients with candidemia should be treated for at least 14 days after negative blood cultures.
 - Patients with prior azole therapy should be treated with an echinocandin for subsequent fungal (especially *C. albicans*) infections.

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

INTRODUCTION

Candida species (spp) have emerged as the fourth most common bloodstream pathogen in the critically ill with an associated mortality rate of 19-50% (1-3). The importance of early detection and appropriate management of *Candida spp* infections cannot be overemphasized. Definitive diagnosis of disseminated fungal infection is frequently made postmortem. Only 50% of patients develop positive blood cultures and less than 40% are diagnosed early enough to institute appropriate antifungal therapy (4). In immunocompromised patient, *Candida spp* are the most commonly isolated fungal pathogen (5).

Particularly with *Candida spp*, differentiating between colonization and infection is often difficult. Gastrointestinal tract colonization with *Candida spp* is the most frequent source with 30-55% of healthy adults demonstrating oropharyngeal colonization and 40-65% fecal colonization (5). Additionally, there are few recognized standards for significant colony counts. Kozinn et al. recommends that a colony count of >10,000 colony forming units (CFU)/mm³ in urine cultures is significant for infection (6). Kozinn et al. also tried to identify a significant colony count for bronchiolar alveolar lavage cultures; while they recommend considering infection to be >100,000 CFU, a histologic diagnosis is still the gold standard (6). Significant colony counts for intracutaneous segment cultures, tissues cultures, or sputum cultures have not been well defined (5). Positive cultures from sterile sites (i.e., blood cultures, urine cultures, etc.) should be considered an infection (5).

It is generally agreed that patients with candidemia or histologically proven disseminated candidiasis should receive antifungal therapy (1,3-7). In the critically ill patient, however, colonization can lead to development of candidemia and/or disseminated fungal infection with increased morbidity and mortality (1,3,5,8).

Treatment of *Candida spp* should be started as soon as possible. Identification of the type of *Candida spp* targeted is essential in ensuring that the appropriate antifungal therapy has been initiated (1,5,7,8). Historically, antifungal therapy was limited to amphotericin B. The use of amphotericin B has been associated with significant morbidity which has led to the widespread use of fluconazole for empiric antifungal therapy. Fluconazole provides excellent *Candida spp* coverage (with a few exceptions) and is well tolerated. However, particularly in the intensive care unit, the landscape of *Candida spp* infections in the ICU is changing as a greater number of non-*albicans* *Candida spp* are isolated leading to issues of fluconazole resistance (1,5,7,8).

LITERATURE REVIEW

Risk Factors

Several different studies have attempted to define risk factors for the development of invasive candidiasis in the intensive care unit. Pappas et al. conducted a prospective, observational study of 1593 adult and pediatric patients with candidemia. They determined that the following risk factors for *Candida* bacteremia were associated with mortality in patients age ≥ 13 years: APACHE II score >18, cancer, urinary catheter, male sex, *Candida parapsilosis* infection, receipt of corticosteroids, and the presence of an arterial catheter (Class II, 9).

McKinnon et al. conducted a prospective study in 301 consecutively treated surgical intensive care unit (SICU) patients to characterize the development or progression of risk factors during a patient's stay in the SICU. They divided risk factors into early (present by SICU Day #3) or late (present on SICU Days #4-8). The following were identified as early risk factors for candidemia: diarrhea, use of total parenteral nutrition (TPN), multiple SICU admissions, multiple surgical procedures, mechanical ventilation, presence of a central venous line (CVL) or a CVL in place > 3 days. Late risk factors included hemodialysis, persistent elevated white blood cell count, hyper- or hypothermia while on antimicrobial therapy, broad-spectrum antimicrobial therapy, solid tumors, and lack of nutritional support (Class II, 10).

Blumberg et al. conducted a multi-center, observational study of all patients admitted to the SICU for > 48 hours. Of the 4276 patients evaluated, 42 developed *Candida* bloodstream infections during the study. Based on multivariate analysis, the following factors were independently associated with an increased

risk of candidemia: prior surgery, acute renal failure, TPN, CVL placement, shock, disseminated intravascular coagulation, treatment with antimicrobial agents that targeted anaerobic organisms (Class II, 11).

Based on the information provided above as well as a number of tertiary references, risk factors for the development of *Candida* infections can be broken down into three components: underlying or pre-morbid conditions, immunologic defects and iatrogenic factors. The risk factors associated with each component are summarized the following table:

Underlying Conditions	Immune Defects	Iatrogenic Factors
- Burns (large $\pm$ inhalation injury) - Cancer <i>Candida</i> colonization - Cytomegalovirus (CMV) - Diabetes mellitus - Graft versus host disease - Hematological malignancies - HIV - Malnutrition - Organ transplantation	- Granulocytopenia - Neutropenia - T-cell defects	- Broad-spectrum antibiotics - Central venous catheters - Chemotherapy - High-dose steroids - Immunosuppressive therapy - Intra-abdominal surgery - Total parenteral nutrition

(Adapted from references 5 & 9-11.)

Candida speciation & role in anti-fungal selection

Candida albicans is the most commonly isolated *Candida* spp. In 2003, 62.3% of cases of invasive candidiasis were attributable to *C. albicans* (Class III, 12). However, the increasing emergence of non-*albicans* *Candida* spp. poses a significant threat to an older and more immunocompromised population. *Candida glabrata* (also known as *Torulopsis glabrata*), *Candida tropicalis*, and *Candida parapsilosis* are the most commonly isolated non-*albicans* species (Class II, 9-12). At ORMC, a review of *Candida* isolates from blood and urine cultures from July 2006 through June 2007 revealed a nearly 50:50 split *C. albicans* to non-*albicans* (52% *C. albicans*, 48% *Candida* non-*albicans*) (13).

The concern with the increasing number of *Candida* non-*albicans* species is that anti-fungal susceptibility patterns vary based on the specific *Candida* spp. For example, *C. krusei* is intrinsically resistant to fluconazole and *C. glabrata* exhibits dose-dependant susceptibility to fluconazole (i.e., requires higher doses to effectively treat) (1). Identifying the specific species of *Candida* isolated makes a significant impact on antifungal therapy decisions. The following table reflects the susceptibility profiles of the more common *Candida* spp which were compiled from a number of prospective and retrospective epidemiology and *in vitro* studies (Class II, 1, 5, 9).

Species	Polyene	Azole			Echinocandin	
	Ampho B	Flucon	Vori	Posa	Caspo	Anid
<i>C. albicans</i>	S	S	S	S	S	S
<i>C. glabrata</i>	S to I	S-DD to R	S – S-DD	S – S-DD	S	S
<i>C. krusei</i>	S to I	R	S – S-DD	S – S-DD	S	S
<i>C. lusitanae</i>	R	S	S	S	S	S
<i>C. parapsilosis</i>	S	S	S	S	I	I
<i>C. tropicalis</i>	S	S	S to I	S	S	S

Ampho B = amphotericin B, Flucon = fluconazole, Vori = voriconazole, Posa = posaconazole, Caspo = caspofungin, Anid = anidulafungin. S = sensitive, S-DD = sensitive dose-dependent, I = intermediate, R = resistant

Resistance of *C. albicans* to fluconazole has been well documented in the HIV population secondary to multiple courses of fluconazole. This has also been demonstrated in the ICU. Particularly for *C. albicans*, fluconazole remains appropriate for initial therapy, but subsequent requirements for empiric or therapeutic

antifungal treatment should employ either a higher dose or an alternative agent, such as an echinocandin (Class III, 1,5,14).

Colonization in Critically Ill Patients

Pittet et al. prospectively determined the relationship between yeast colonization and subsequent infection in critically ill patients. Routine cultures of the oropharynx/trachea and stomach were obtained. Colonization was defined as the presence of *Candida* in three or more samples taken from the same or different body site on at least two consecutive screening days. Twenty-nine patients who were colonized with *Candida spp* were enrolled in the study and 11/29 (38%) developed *Candida* infections. The patients who developed severe *Candida* infections were found to have had a significantly longer duration of antibiotic exposure, higher APACHE II scores and had a greater intensity of *Candida* colonization as compared to the 18 patients who did not develop *Candida* infections. Multiple logistic regression identified APACHE II score and intensity of *Candida* colonization as independent predictors of infections ($p < 0.001$). Genotyping revealed that all patients who developed severe infections were previously colonized with an identical strain (Class II, 15).

Candidemia

Candidemia and invasive candidiasis encompass a wide variety of *Candida spp* infections ranging from bloodstream infections to deep tissue and organ infections (1). Candidemia is the fourth most common nosocomial bloodstream infection in the United States (16). The attributable mortality rate is 33-47% for invasive *Candida* infections, which is significantly higher than the mortality rate for the other major causes of nosocomial bloodstream infections (17).

Only 50% of patients with invasive candidiasis will have positive blood cultures. Febrile patients with a single positive blood culture should be considered to have disseminated infection (5). Treatment should be targeted at the *Candida spp* isolated (Class II, 5,9).

Treatment of candidemia should include changing out or removal of all invasive devices including central lines. Repeat blood cultures should be obtained after 3-5 days of therapy to assess clearance of the organism from the bloodstream. Treatment should be continued for at least 14 days after negative blood cultures are obtained (Class III, 5).

Central venous catheters are well documented as independent risk factors for the development of candidemia (1,5,9-11). Invasive devices can serve as the primary source of invasive *Candida spp* infections. *C. albicans* and *C. parapsilosis* are the most commonly associated *Candida spp*. with the production of biofilms on invasive devices, which renders them nearly completely resistant to antifungal therapy. Treatment of candidemia associated with biofilm production is limited to amphotericin B lipid formulations or the echinocandins (18)

The role of central venous catheter (CVC) removal in the treatment of candidemia remains controversial. Raad et al. reviewed the timing of catheter removal in cancer patients with candidemia. The authors found that removal of the CVC within 72 hours after diagnosis of candidemia was associated with improved response to antifungal therapy (Class III, 19). Rodriguez et al. investigated whether early (< 24 hours) versus late (> 24 hours) removal of the CVC after diagnosis of candidemia affected mortality and found no difference between the two groups. The authors noted that surgical patients, ICU patients, and patients with a high severity of illness were more likely to have early catheter removal (Class III, 20).

Peritoneal Candidiasis

Solomkin et al. retrospectively identified 56 cases of *Candida* peritonitis. Thirty cases occurred as a result of spontaneous disease and 26 occurred following elective surgery. Gastroduodenal ulcer perforation was the initiating event in 50% of patients with spontaneous disease. Anastomotic breakdown or intestinal necrosis was identified upon re-exploration in 73% of patients who initially had elective surgery. Overall mortality was 71%. For those patients who underwent autopsy, unrecognized disseminated *Candida* infection was the cause of death in approximately one-third of cases. The presence of candidemia was associated with an 85% mortality rate. All patients had positive cultures at other sites prior to the development of candidemia (Class III, 21).

Rutledge et al. retrospectively studied *Candida*-positive peritoneal fluid (Group I, n=39) or intra-abdominal abscess cultures (Group II, n=24). The source of peritoneal contamination included various sites along the gastrointestinal (GI) tract, with small bowel injury being the most common in both groups. No patient in Group I received antifungal therapy with only 1 patient (2.6%) developing an abscess, which was successfully managed with surgical drainage. Twenty of 24 patients in Group II were managed with surgical drainage and no antifungal therapy. Mortality was 30% (6/20) in the patients who received no antifungal therapy, although only 1 death was attributable to *Candida* infection. The remaining patients (4/24) received antifungal therapy in addition to surgical drainage. Mortality among the 4 patients treated with antifungal therapy was 50% (2/4) but, again, only one death was presumably related to *Candida* infection (Class III, 22).

Calandra et al. performed a two-part study to determine the significance of *Candida* isolated from intra-abdominal cultures, identify risk factors for intra-abdominal *Candida* infection, and determine appropriate therapy. Patients in whom *Candida* was isolated from an intra-abdominal culture or abdominal drain were identified. Data was collected retrospectively for six months and prospectively for the following 18 months. *Candida spp* were considered pathogenic when isolated from a patient with peritonitis or an abscess after abdominal surgery. If isolated from a polymicrobial culture, the *Candida spp* was considered pathogenic only when a blood culture was positive or the patient's condition failed to improve with surgical drainage and antibiotics. Of the 49 patients identified, *Candida* was considered pathogenic in 19 (Group A) and non-pathogenic in 30 (Group B). GI perforation was the underlying surgical disorder in 9/19 (32%) of Group A patients and 19/30 (68%) of Group B patients. All patients in Group A had recurrent perforations necessitating multiple surgical procedures. In contrast, the majority of the Group B patients underwent a single operation. All patients in Group B recovered without antifungal administration. Only 3/19 (16%) of the Group A patients recovered with surgical drainage alone. The remainder either recovered with a combination of repeat surgical management and antifungal therapy (9/19, 47%) or died from uncontrolled infection (6/19, 32%). Moderate to heavy growth of *Candida* in the first positive culture was significantly more prevalent in Group A patients. Infectious mortality was also significantly higher in Group A patients (42% versus 3%, p=0.002) (Class III, 23).

Eggimann et al. conducted a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of fluconazole for the prevention of intra-abdominal *Candida* infections in high-risk surgical patients. Patients with recent abdominal surgery and who had recurrent GI perforations or anastomotic leaks (suspected or confirmed) were eligible for enrollment. Fluconazole was continued until complete resolution of the intra-abdominal disease, development of *Candida* infection, or drug-related adverse event. Infection was defined as the presence of intra-abdominal candidiasis, candidemia, *Candida* urinary tract infection, or biopsy-proven tissue invasion. Forty-three patients were evaluated (23 fluconazole, 20 placebo). The median APACHE II score for both group was 13. *Candida* colonization at baseline was present in 44% (10/23) of the fluconazole patients and 35% (7/20) of the placebo patients (p=0.02). *Candida* peritonitis occurred in 4% (1/23) of the patients on fluconazole as compared to 35% (7/20) patients on placebo (p=0.02). Overall, there was no significant difference in the number of *Candida* infections between the two groups (2 in the fluconazole group, 7 in the placebo group, p=0.06). Patients in the fluconazole group had a longer disease-free interval (p=0.04). The authors concluded that fluconazole significantly decreased the rate of *Candida* peritonitis in high-risk GI surgery patients (Class I, 24).

Candiduria

Sobel et al. conducted a prospective, multicenter, placebo-controlled study evaluating the efficacy of fluconazole in patients with asymptomatic or minimally symptomatic candiduria. Candiduria was defined as ≥ 1000 CFU/mL yeast in two consecutive urine cultures. Patients with indwelling catheters were eligible only if candiduria persisted following removal or changing of the catheter. Exclusion criteria included urologic obstruction, neutropenia, or extra-urinary fungal infection. Treatment consisted of fluconazole (400mg loading dose, then 200mg q24) or placebo for 14 days. 316 patients were evaluated – primarily elderly and with recent antibiotic exposure, approximately half of which were catheterized or diabetic. *C. albicans* accounted for ~50% of the cases in both groups. *C. glabrata* was isolated in 18% of fluconazole patients and 24% of placebo patients. At the end of therapy, eradication rates were significantly greater in the fluconazole group as compared to the placebo group (63% vs. 39%, p=0.004).

Mycologic cure occurred in only 20% of those managed with a catheter change alone (Class I, 25).

Nassoura et al. performed a two-part study to investigate the role of fluconazole in surgical ICU patients with candiduria ($>100,000$ CFU/mL). Part I was retrospective and included 27 patients with candiduria. All patients were treated with amphotericin B bladder irrigation for 7 days. Part II was prospective and included 20 patients with candiduria and systemic evidence of sepsis who were treated with fluconazole (200mg daily). In the retrospective analysis, 63% of patients developed disseminated infection in spite of the bladder irrigation. Of these patients, 59% developed candidemia, and 53% died of multi-organ system failure and sepsis. No patients in the prospective analysis developed disseminated *Candida* infections and this group only had a 5% mortality rate (Class II, 26).

Antifungal Therapy for Candidemia & Invasive Candidiasis

Rex et al. conducted a prospective, randomized, double-blind, multicenter, noninferiority trial comparing fluconazole with amphotericin B in the treatment of candidemia. They enrolled 237 patients who had been diagnosed with candidemia or invasive candidiasis within the past 4 days. Patients were treated with either fluconazole 400mg (or 6mg/kg if >90 kg or <50 kg) IV daily or amphotericin B 0.5-0.6mg/kg IV daily. After 7 days of IV therapy, patients were switched to either oral fluconazole or three-times weekly amphotericin B. The primary endpoint was efficacy defined as success, failure, or relapse. 224 patients were included in the intention-to-treat analysis. Treatment success was 70% in the fluconazole group and 79% in the amphotericin B group. 15% of the fluconazole patients and 12% of the amphotericin B patient failed therapy. Fluconazole was deemed to be noninferior to amphotericin B for the treatment of candidemia or invasive candidiasis (Class I, 27).

In another study, Rex et al. compared fluconazole plus placebo versus fluconazole plus amphotericin B for the treatment of candidemia in non-neutropenic patients. This was a randomized, blinded, multi-center trial conducted due to a theoretical concern that the combination of fluconazole plus amphotericin B was antagonistic. 236 patients were enrolled; all of whom were diagnosed with candidemia within the past 4 days. Patients received fluconazole 800mg (or 12mg/kg if >90 kg or <50 kg) IV daily with or without amphotericin B 0.6-0.7 mg/kg IV daily. All patients were pre-treated with diphenhydramine and acetaminophen or ibuprofen before either the amphotericin B or the placebo infusion. After 5 days of IV therapy, fluconazole was switched oral/enteral route (same dose). The primary endpoint was time to treatment failure, with a secondary endpoint of treatment success. Treatment success occurred in 56% of the patients treated with fluconazole alone and 69% of the fluconazole plus amphotericin B patients ($p=0.043$). In the fluconazole alone group, 17% of the patients failed to clear their bloodstream as compared to 6% in the combination group. Of note, 23% of the patients receiving combination therapy required dose adjustment for renal dysfunction as compared to fluconazole alone ($p<0.001$); changes in liver function tests were comparable between the two groups. Overall, the combination of fluconazole plus amphotericin B is not antagonistic and may lead to more rapid blood stream clearance. One limitation of this study is that the patients in the fluconazole plus placebo group had a higher APACHE II score as compared to the fluconazole plus amphotericin B group (16.8 vs 13) raising concern for the validity of the results (Class I, 28).

Mora-Duarte et al. compared caspofungin with amphotericin B for the treatment of invasive candidiasis in a randomized, double-blind, multicenter noninferiority trial. They enrolled 239 patients, 224 of which were included in the intention-to-treat analysis (89% of the population was non-neutropenic). All of the patients were diagnosed with candidemia or invasive candidiasis in the previous 4 days. Patients were treated with either caspofungin (70mg IV x 1, then 50mg daily) or amphotericin B (0.6-0.7mg/kg (non-neutropenic) or 0.7-1 mg/kg (neutropenic) IV daily). After 10 days of IV therapy, patients could be switched to oral fluconazole. The primary endpoint was clinical and microbiologic response at the end of IV therapy. 73.4% of the patients in the caspofungin group and 61.7% of the patients in the amphotericin B group were successfully treated. Adverse events in the caspofungin group were significantly lower than in the amphotericin B group (2.6% vs. 23.2% respectively, $p=0.003$). Caspofungin was deemed to be noninferior to amphotericin B for the treatment of candidemia or invasive candidiasis (Class I, 29).

Kullberg et al. conducted a randomized, multicenter, noninferiority trial comparing voriconazole versus amphotericin B plus fluconazole for the treatment of candidemia. 422 patients were enrolled, 370 of which

were included in the intention-to-treat analysis. Patients were randomly assigned in a 2:1 ratio to receive either voriconazole (6mg/kg IV x 2doses, then 3mg/kg IV q12h x at least 2 days, then 200mg po q12h) or amphotericin B (0.7-1mg/kg IV daily x at least 3 days) followed by fluconazole (400mg IV/po daily). The primary endpoint was efficacy defined as clinical and microbiologic response at 12 weeks. For patients who followed up at 12 weeks (370 total), 41% of patients in both groups were successfully treated. Based on the intention-to-treat analysis, treatment success was still similar in both groups (65% with voriconazole, 71% with amphotericin B plus fluconazole, p=0.25). Adverse events were significantly higher in the amphotericin B plus fluconazole group as compared to the voriconazole group (14% vs 4%, p=0.0004). Based on this information, voriconazole was deemed to be noninferior to amphotericin B plus fluconazole for the treatment of candidemia (Class I, 30).

COST COMPARISON (acquisition cost)

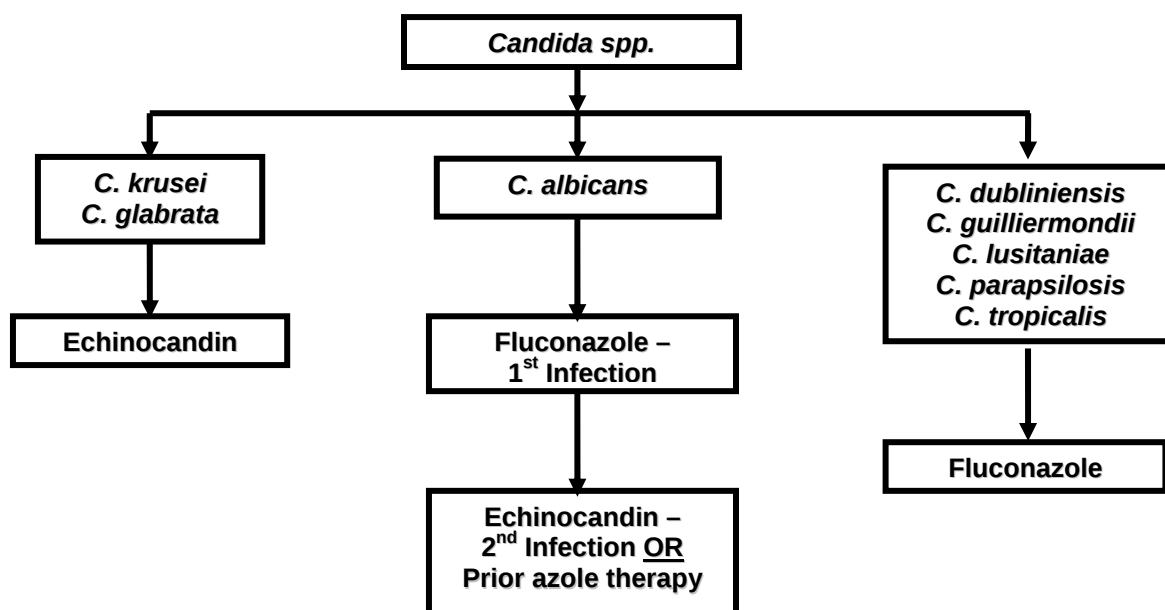
	Fluconazole	Voriconazole*	Caspofungin
Usual Dose	800mg IV x 1, then 400mg IV daily OR 400mg po daily	6mg/kg IV q12 x2, then 4mg/kg IV q12 OR 4mg/kg po q12	70mg IV x 1, then 50mg IV daily
Cost	800mg IV = \$17.46 400mg IV = \$8.73 400mg po = \$0.76	6mg/kg 400mg = \$187.24 4mg/kg 300mg IV = \$140.46 300mg po = \$50.25	70mg IV = \$118.24 50mg IV = \$118.24

*Cost estimates based on 70kg patient

SPECIFIC ANTIFUNGAL TREATMENT CONSIDERATIONS:

- **Candidemia/Invasive Candidiasis:**
 - o For the first infection with all *Candida spp* except *C. glabrata* & *C. krusei*, use fluconazole as first line
 - o For patients on amiodarone, use caspofungin as first line
 - o For subsequent infections, unresolved infections, or patients with renal failure, use caspofungin
- **Candiduria:**
 - o For azole-resistant *Candida spp* and concern for disseminated infection, intravenous amphotericin B is recommended
 - o For local infection with azole-resistant *Candida spp*, amphotericin B bladder irrigation is recommended
 - o Echinocandins & voriconazole are NOT recommended due to limited urinary excretion (<5% of active drug)

Targeted Antifungal Recommendations for Candidemia & Invasive Candidiasis



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