CANDIDA INFECTION MANAGEMENT IN SURGICAL PATIENTS

SUMMARY

Candida infections are associated with significant mortality. Patents with microbiologic evidence of candidemia or disseminated canididiasis 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**
  - Fluconazole and echinocandins may be used as first line for treatment of *Candida* infections.
- **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 TWO or more risk factors.
  - Identification of all *Candida spp.* is required to ensure appropriate antifungal therapy.
  - Surgical debridement and/or drainage of localized fungal infections should be performed.
  - For the first infection with all *Candida spp* except *C. glabrata* and *C. krusei*, use fluconazole as first line.
  - Echinocandins should be considered for patients in septic shock. For *C. glabrata* and *C. krusei*, use echinocandins as first line.
    - For infections due to *C. glabrata*, patients may receive high-dose fluconazole or voriconazole as an alternative, if susceptible.
    - For infections due to *C. krusei*, voriconazole may be considered as an alternative
  - Transition from intravenous therapy to oral/enteral fluconazole or voriconazole in patients who are clinically stable, have susceptible isolates, and negative repeat blood cultures.
- **Level 3**
  - Critically ill patients with hemodynamic instability (septic shock) initiated on empiric antifungal therapy should receive an echinocandin.
  - Initiate antifungal therapy following gastrointestinal perforation in the presence of peritonitis and one or more risk factors.
  - 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 until susceptibilities return for azole antifungals.

INTRODUCTION

Candida species (spp) have emerged as the seventh most common health care-associated pathogen in the critically ill with an associated mortality rate of 19-50% (1-4). 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

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.

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cultures and less than 40% are diagnosed early enough to institute appropriate antifungal therapy (5). In immunocompromised patient, *Candida spp* are the most commonly isolated fungal pathogen (6).

Differentiating between colonization and infection, particularly with *Candida spp,* 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 (6). Additionally, there are few recognized standards for significant colony counts. Colony counts in the urine and the sputum or bronchoalveolar lavage (BAL) cannot be used to define infection (7). Significant colony counts for intracutaneous segment cultures, tissues cultures, or sputum cultures have not been well defined Thus, only positive cultures from sterile sites (i.e., blood cultures) should be considered an infection unless the patient is symptomatic (6).

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 (1,3,6,8). If invasive candidiasis is suspected, 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, total parenteral nutrition (TPN), CVL placement, shock, disseminated intravascular coagulation (DIC), and 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
• Acute renal failure • Burns (large ± inhalation injury) • Cancer • *Candida* colonization • Cytomegalovirus (CMV) • Diabetes mellitus • Diarrhea • DIC • Graft versus host disease • Hematological malignancies • HIV • Malnutrition • Organ transplantation	• Granulocytopenia • Neutropenia • T-cell defects	• Broad-spectrum antibiotics • Central venous catheters • Chemotherapy • Hemodialysis • High-dose steroids • Mechanical ventilation • Multiple SICU admissions • Immunosuppressive therapy • Intra-abdominal surgery • Thoracic surgery • Total parenteral nutrition

(Adapted from references 5 & 9-11.)

<u>*Candida* speciation & role in anti-fungal selection</u>

Candida albicans is the most commonly isolated *Candida spp.* In 2009, 48.4% 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).

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 in most patients, 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, 1,5,13). Once susceptibilities return, definitive therapy can be deescalated to fluconazole, if susceptible and the patient is clinically stable with repeat blood cultures negative (7).

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, 7, 9, 14).

	Azoles				Polyene	Echinocandins		
Species	**Fluc**	**Vori**	**Posa**	**Isavu**	**Ampho B**	**Caspo**	**Anid**	**Mica**
C. albicans	S	S	S	S	S	S	S	S
C. glabrata	**S-DD to R**	**S-DD to R**	**S-DD to R**	S	S	S	S	S
C. krusei	**R**	**S**	**S**	S	S	S	S	S
C. lusitaniae	S	S	S	S	**R**	S	S	S
C. parapsilosis	S	S	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S	S	S

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

<u>Colonization in Critically Ill Patients</u>

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).

Leon et al. conducted a prospective, cohort, observational, multicenter surveillance study of fungal infections and colonization in 1699 nonneutropenic critically ill patients. A logistic regression model was utilized to determine predictors for proven candidal infection. The "Candida Score" was developed to determine which patients will benefit from early antifungal administration. A "Candida Score" of >2.5 helps differentiate patients who may benefit from treatment for invasive fungal infections with 81% sensitivity and 74% specificity. The "Candida Score" is calculated using the rubric below: (Class II, 16)

Predictor	**Points**
Surgery during ICU admission	1
Multifocal colonization with Candida	1
Total parenteral nutrition	1
Septic shock	2

Nonculture Positive Diagnostic Tools

There has been increasing utilization of alternative diagnostic tools in order to determine which patients may be suffering from an active candidal infection. For example. *B*-D-glucan, a cell wall component of *Candida* species, *Aspergillus* species, *Pneumocystis jiroveci* and other fungi can now be detected with a serum assay. This assay may be used as an adjunct to cultures to identify cases of invasive candidiasis prior to the return of positive blood cultures, thereby, shortening the time to initiation of antifungal therapy. However, this assay has poor specificity and false positivity especially in critically ill patients. The assay may be affected by antibiotics, hemodialysis, bacterial infections, and blood products. Therefore, this assay may be used as a positive predictor, but caution should be taken when interpreting results of the assay. Alternatively, a *Candida* polymerase chain reaction (PCR) may also be useful for early detection of invasive candidiasis within 6 hours of testing and initiation of antifungal therapy. Additionally, the T2Candida assay was developed to identify *Candida spp.* in whole blood in approximately 3 hours. However, little data has been published evaluating the use of *Candida* PCRs and the T2Candida assay and thus, their role in diagnosis of *Candida* infections is not well established (Class II, 17-19).

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 (20).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 (9).

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). Kollef et al. conducted a retrospective cohort study of hospitalized patients with septic shock and blood cultures positive for *Candida* species in 224 patients. In-hospital mortality was 63.5% with delayed antifungal treatment and failure to achieve timely source control as risk factors for mortality. In patients with adequate source control and antifungal therapy administered within 24 hours of onset of shock, mortality was 52.8%, compared to a mortality rate of 97.6% in patients who did not have early source control or antifungal administration (21).Treatment of candidemia should include changing out or removal of all invasive devices including central lines. Repeat blood cultures should be obtained every day or every other day 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, 7). Computed tomographic or ultrasound imaging of the genitourinary tract, liver, and spleen

should be performed if blood cultures are persistently positive for *Candida* in order to assess risk for metastatic complications and determine duration of therapy (7). Additionally, a transesophageal echocardiogram may be considered if blood cultures are persistently positive in order to evaluate for signs of endocarditis (22).

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 (23). 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, 24). CVCs should be removed as early as possible especially if presumed to be the source of infection (7).

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, 25).

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, 26).

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 anastamotic 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, 27).

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, than 200mg q24) or placebo for 14 days. This study evaluated 316 patients, primarily elderly and with recent antibiotic exposure, and 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, 28).

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, 29).

Overall, treatment of asymptomatic candiduria is not recommended unless the patient is at high risk of dissemination, a high risk neutropenic patient, or undergoing urologic surgery. Fluconazole 6 mg/kg IV/PO daily is recommended first line for treatment of asymptomatic candiduria in select patients. Amphotericin deoxycholate 0.3-0.6 mg/kg IV daily may be considered as an alternative for urinary tract involvement, if fluconazole is not an option (7)

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 >90kg or <50kg) 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. The study included 224 patients in the intention-to-treat analysis. Treatment success was 70% in the fluconazole group and 79% in the amphotericin B group. Approximately 15% of the fluconazole patients and 12% of the amphotericin B patients failed therapy. Fluconazole was deemed to be noninferior to amphotericin B for the treatment of candidemia or invasive candidiasis (Class I, 30).

Kullberg et al. conducted a randomized, multicenter, noninferiority trial comparing voriconazole to amphotericin B plus fluconazole for the treatment of candidemia. This study enrolled 422 patients, 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, 31). Fixed dose voriconazole at 200 mg PO BID may be preferred for longer durations as higher weight-based doses of voriconazole and longer durations of

therapy may be associated with hepatotoxicity (32). In addition, voriconazole IV has the potential for cyclodextrin accumulation and nephrotoxicity in patients with renal dysfunction with a creatinine clearance <50 mL/minute. Voriconazole is also associated with visual side effects, photosensitivity, periostitis, and central nervous system effects making it a less preferable agent to fluconazole in susceptible isolates (7).

Alternatively, 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, 33).

In a double-blind, randomized, multinational, non-inferiority study, Kuse et al. compared initial dosing of micafungin 100 mg IV daily (weight >40 kg) or 2 mg/kg (weight ≤40 kg) to liposomal amphotericin B 3 mg/kg IV daily for the treatment of candidemia and invasive candidiasis. This study enrolled 267 adult patients who had one or more positive cultures for candida in the blood or another sterile site. Patients who had evidence of radiographic abnormalities received micafungin 200 mg IV daily and amphotericin B 5 mg/kg IV daily. Most patients received between 14 days to 4 weeks of therapy. However, patients with evidence of chronic disseminated candidiasis, candida osteomyelitis, or candida endocarditis were treated for up to 8 weeks. The median dose and duration of therapy for micafungin was 100 mg IV daily for about 15 days and amphotericin B 3 mg/kg IV daily for about 15 days. There was no difference in the rate of successful treatment between micafungin and liposomal amphotericin B (74.1% versus 69.6%). However, significantly more patients in the amphotericin B group experienced adverse effects including rigors, back pain, elevated creatinine, and infusion-related reactions (34).

In 2007, Pappas et al. compared micafungin to caspofungin in an international, randomized, double-blind trial in patients with candidemia or invasive candidiasis. A total of 595 patients with at least 1 positive blood culture for *Candida* or a diagnosis of noncandidemic invasive candidiasis were included in the study. Patients were randomized to receive micafungin 100 mg IV daily, micafungin 150 mg IV daily or caspofungin 70 mg IV x1, then 50 mg IV daily for 14-28 days or up to 8 weeks in patients with disseminated candidiasis or *Candida* endopthalmitis. Patients were permitted to switch to oral fluconazole 400 mg PO daily after a minimum of 10 days of IV therapy if the isolate was susceptible to fluconazole. The median duration of therapy was 14 days and approximately 19% of patients in the study received oral fluconazole step-down therapy. There was no difference in treatment success between micafungin 100 mg IV daily (76.4%), micafungin 150 mg IV daily (71.4%), and caspofungin (72.3%) including patients who received oral step-down therapy (35).

Reboli et al. conducted a randomized, double-blind, noninferiority study in adult patients with candidemia or invasive candidiasis with at least one positive blood culture or culture obtained from a sterile site. They enrolled 245 patients who received anidulafungin 200 mg IV x1, then 100 mg IV daily or fluconazole 800 mg IV x1, then 400 mg IV daily followed by oral fluconazole 400 mg PO daily after 10 days of IV therapy. At the end of IV therapy treatment was successful in 75.6% of patients treated with anidulafungin and 60.2% of patients treated with fluconazole (p=0.01). There was no difference in the frequency and types of adverse events or rate of death from all causes (p=0.13). Anidulafungin was deemed to be noninferior to fluconazole for the treatment of candidemia or invasive candidiasis (Class I, 36).

An open-label, non-comparative study conducted in 282 patients evaluated the use of anidulafungin 200 mg x1, then 100 mg IV daily for 4 days followed by step-down to oral azole therapy with fluconazole or voriconazole for the treatment of candidemia and invasive candidiasis with susceptible isolates. Of the 60% of patients that received step-down therapy, 83.7% had an overall successful response. The authors

concluded that oral step-down therapy was efficacious for the treatment of susceptible *Candida* infections and should be considered in all patients to reduce cost and hospital length of stay (37).

DAILY COST COMPARISON (acquisition cost)

	Fluconazole	Voriconazole	Micafungin[+]	Caspofungin	Anidulafungin
Usual Dose	800 mg IV (12 mg/kg) x 1, then 400 mg (6 mg/kg) IV OR 400 mg PO daily	6 mg/kg IV q12 x2, then 4 mg/kg IV q12 OR 4 mg/kg PO q12	100 mg IV daily	70 mg IV x1, then 50 mg IV daily	200 mg IV x1, then 100 mg IV daily
Daily Cost*	800 mg IV = $7.38 400 mg IV = $3.69 400 mg po = $3.32	~6 mg/kg 400 mg = $128.32 ~4mg/kg 200 mg IV = $64.16 200 mg PO = $37.02	100 mg IV = $34.91	70 mg IV = $319.16 50 mg IV = $319.16	200 mg IV = $137.14 100 mg IV = $68.57

*Cost estimates based on 70 kg patient
[+] Preferred agent for Orlando Health

SPECIFIC ANTIFUNGAL TREATMENT CONSIDERATIONS:

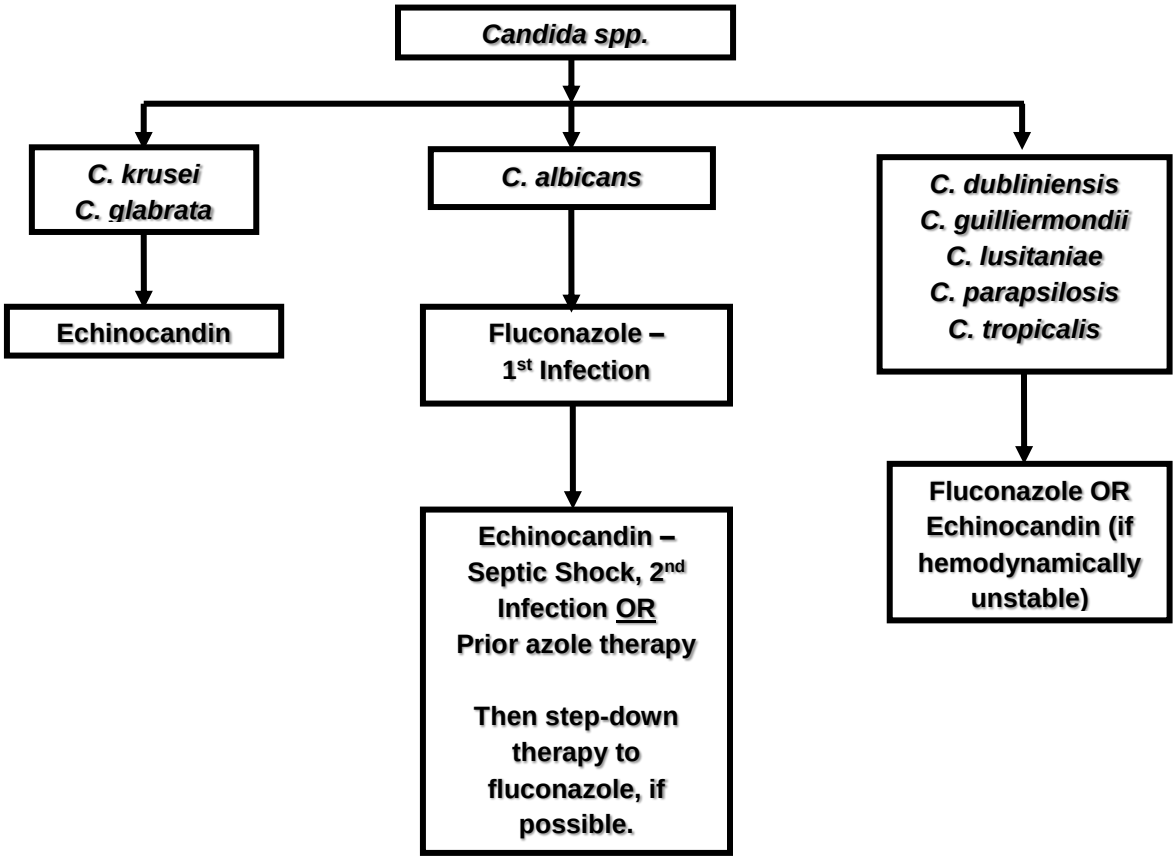
- **Candidemia/Invasive Candidiasis:**
  - In critically ill patients that are in septic shock, echinocandins (micafungin 100 mg IV every 24 hours) are preferred over fluconazole for empiric antifungal therapy.
  - Fluconazole 6 mg/kg dosing is now preferred with doses rounded to the nearest 100 mg
  - For the first infection with all *Candida spp* except *C. glabrata* and *C. krusei*, use fluconazole as first line. Echinocandins should be considered for patients in septic shock.
  - For *C. glabrata* and *C. krusei*, use echinocandins as first line.
  - For patients on amiodarone, use echnocandins as first line.
  - For subsequent infections or unresolved infections, use an echinocandin for definitive therapy, but fluconazole may be used for step-down therapy, if susceptible.
  - For infections due to *C. glabrata*, echinocandins are first line, but patients may receive high dose fluconazole or voriconazole as an alternative, if susceptible. Fluconazole is preferred over voriconazole whenever possible.
  - For infections due to *C. krusei*, voriconazole may be considered as an alternative to echinocandins.
  - Transition from IV therapy to oral fluconazole or voriconazole in patients who are clinically stable, have susceptible isolates, and negative repeat blood cultures. Voriconazole can be considered in certain cases where isolates are resistant to fluconazole.

- **Peritoneal Candidiasis:**
  - Initiate antifungal following gastrointestinal perforation in the presence of peritonitis and one or more risk factors.
  - Fluconazole should be considered for the prevention of intra-abdominal *Candida* infections in high-risk surgical patients including those with recent abdominal surgery or recurrent gastrointestinal perforations or anastomotic leaks.

- **Candiduria:**
  - For susceptible *Candida* spp, use fluconazole as first line.
  - Echinocandins may be considered for the treatment of pyelonephritis or disseminated infection, although urinary excretion is limited (<5% active drug).
  - For azole-resistant *Candida spp* and concern for disseminated infection, intravenous amphotericin B is recommended.
  - For local infection with azole-resistant *Candida spp*, amphotericin B bladder irrigation is recommended.

- Voriconazole is not recommended due to limited urinary excretion (<5% of active drug).

Targeted Antifungal Recommendations for Candidemia & Invasive Candidiasis



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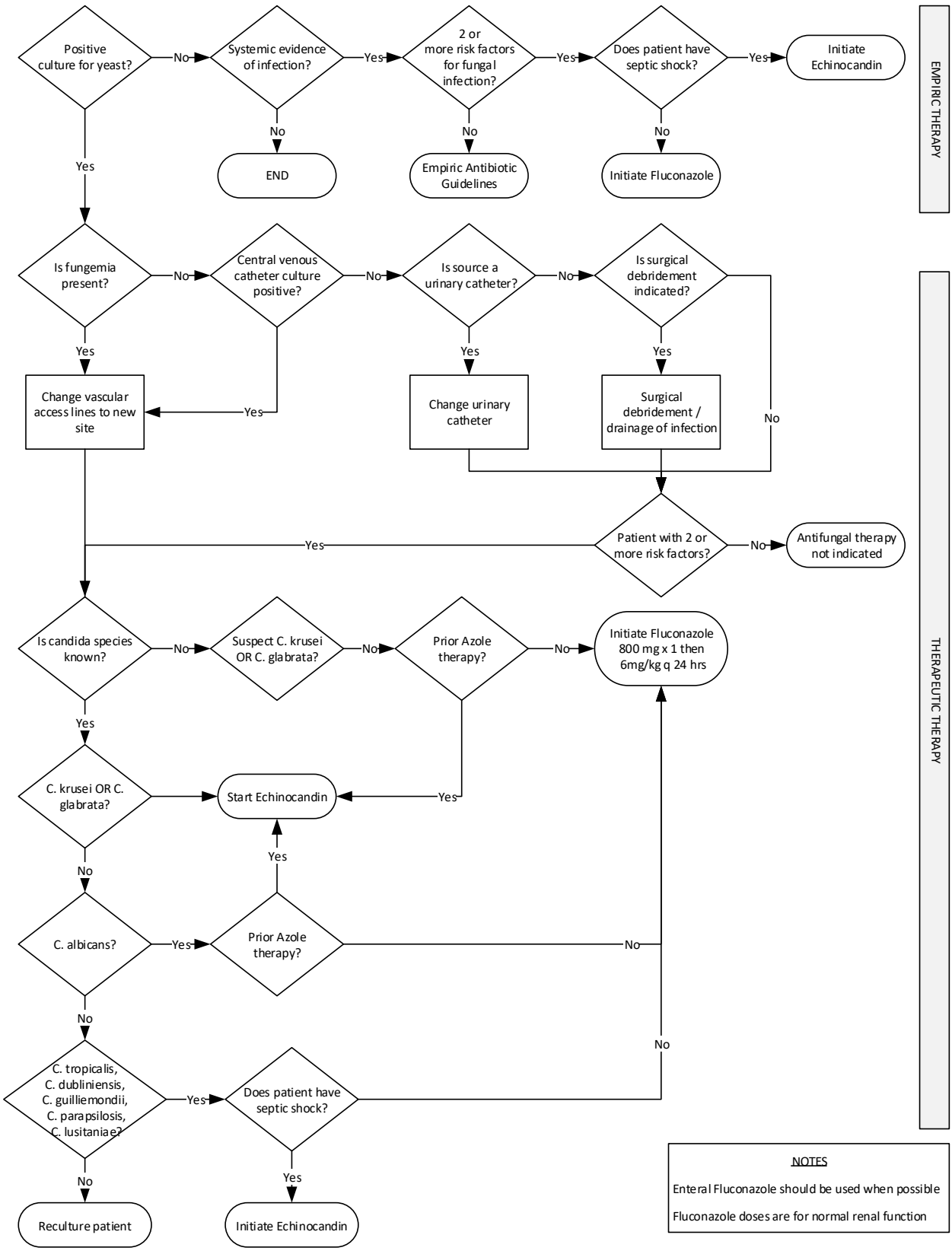

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