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 bacterial infection, two or more risk factors for fungal infection, and an inadequate clinical response to antibiotics. Empiric therapy should also be administered following gastrointestinal perforation in patients with risk factors.

RECOMMENDATIONS
• Level I
  ➢ None

• Level II
  ➢ All patients with fungemia should be treated with a systemic antifungal agent.
  ➢ Central venous and urinary catheters should be changed if they culture positive for yeast.
  ➢ Surgical debridement and/or drainage of localized fungal infections should be performed where possible.
  ➢ Persistent candiduria following catheter change or removal should be treated with a systemic antifungal agent.
  ➢ Empiric fluconazole should be considered in patients with systemic evidence of infection, 2 or more risk factors, AND an inadequate response to appropriate antibiotic therapy.

• Level III
  ➢ Central venous catheters should be changed when fungemia is identified.
  ➢ Critically ill patients who have a positive culture for yeast and at least 1 risk factor should receive a systemic antifungal agent.
  ➢ Candiduria in the presence of a structural abnormality or obstruction of the urinary tract or immunosuppression should be treated with a systemic antifungal agent.
  ➢ The enteral route should be used for fluconazole administration wherever possible.
  ➢ Antifungal therapy should be initiated following gastrointestinal perforation in the presence of peritonitis or immunosuppression AND 1 or more risk factors.

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 have emerged as the fourth most common bloodstream pathogen in the critically ill with a mortality rate exceeding 50 percent (1-3). The importance of early detection and appropriate management of candidal infection cannot be overemphasized. Definitive diagnosis of disseminated fungal infection is frequently made postmortem, however, with only 50% of patients demonstrating positive blood cultures and less than 40% being diagnosed early enough to institute appropriate antifungal therapy (4).

Significant fungal cultures are defined as >100,000 colony forming units (CFU) /mm³ for sputum and urine, >15 CFU for intracutaneous segment cultures, and >10,000 CFU for tissue cultures. The presence of “budding yeast” or pseudohyphal forms should raise the clinician’s suspicion for invasive candidiasis. Colonization is defined as recovery of Candida species from one or more sites (other than blood) without signs or symptoms of infection.

It is generally agreed that patients with candidemia or histologically proven disseminated candidiasis should receive antifungal therapy (5). The significance of positive cultures for other fungal species remains controversial, however, as such cultures may represent either disseminated infection or colonization. In the immunologically intact individual, colonization might be considered a benign condition. In the critically ill patient, however, colonization can lead to development of candidemia and/or disseminated fungal infection with increased morbidity and mortality (6-10).

Historically, antifungal therapy was limited to amphotericin B with its significant morbidity and organ dysfunction. Over the past decade, fluconazole has essentially replaced amphotericin B due to its reduced side effect profile and proven therapeutic equivalence. Careful selection of candidates for fluconazole therapy is necessary to minimize overuse and the associated emergence of resistant Candida species. The consequences of widespread fluconazole use are best illustrated in the HIV population, where microbiologic and clinical resistance are well-documented (11). Identification of patients at highest risk for candidemia and disseminated fungal infection is necessary to select the most appropriate candidates for antifungal therapy.

<<Voriconazole>>

Caspofungin, the first agent in a new class of antifungals known as the echinocandins, is indicated for the treatment of candidemia and Candida-associated intra-abdominal abscesses, peritonitis, pleural space infections, and esophageal candidiasis. It is also indicated for the treatment of invasive Aspergillosis infection in patients who are refractory to or intolerant of other therapies. Caspofungin exerts its effects by inhibiting the synthesis of β-(1,3)-D-glucan which is an essential cell wall component of many fungi. Caspofungin, available parenterally only, is given as a 70 mg IV loading dose on day 1, followed by 50 mg IV daily. It is not necessary to adjust the dose in elderly patients, those with renal dysfunction, or those with mild hepatic impairment (defined as a Child-Pugh score 5-6). In patients with moderate hepatic impairment (defined as a Child-Pugh score 7-9), the maintenance dose should be reduced to 35 mg IV daily. Caspofungin is generally tolerated well, with the most commonly reported adverse effects being chills, fever, phlebitis, tachycardia, nausea, vomiting, rash, abdominal pain, headache and diarrhea.

LITERATURE REVIEW
Risk Factors
Wey et al. retrospectively determined the independent predictors for nosocomial candidemia (6). A multivariate analysis revealed number of antibiotics, isolation of Candida from other sites, hemodialysis, and presence of an indwelling vascular catheter to be predictors of candidemia. Overall mortality was 57% and attributable mortality was 38% (Class III). Bross et al. conducted a similar study in which a central line, indwelling bladder catheter, two or more antibiotics, abnormal serum creatinine, diarrhea, and candiduria where identified as predictors of candidemia (Class II) (12).
Colonization in Critically Ill Patients

Pittet et al. prospectively determined the relationship between yeast colonization and subsequent infection in critically ill patients (9). 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. Thirty-eight percent of patients developed severe Candida infection with a significantly longer duration of antibiotic exposure, higher APACHE II score and greater intensity of Candida colonization than colonized patients. Multiple logistic regression identified APACHE II score and intensity of Candida colonization as independent predictors of infection (p<0.001). Genotyping revealed that all patients who developed severe infection were previously colonized with an identical strain (Class II).

Safran et al. retrospectively investigated the clinical significance of positive candidal cultures in the intensive care units (ICU) (10). Mortality for patients with at least one positive Candida culture was significantly higher than overall mortality for all ICU admissions (42% vs. 11%, p<0.05) (Class III).

Peritoneal Candidiasis

Solomkin et al. retrospectively identified 56 cases of Candida peritonitis (7). 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 candidal 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).

Rutledge et al. retrospectively studied Candida-positive peritoneal fluid (group I, n=39) or intra-abdominal abscess cultures (group II, n=24) (13). The source of peritoneal contamination included various sites along the gastrointestinal (GI) tract, with small bowel injury being 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. Mortality was 30% (6/20), although only 1 death was felt to be related to Candida infection. The remaining patients received antifungal therapy in addition to surgical drainage. Mortality was 50% (2/4), with 1 death presumably related to fungal infection (Class III).

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 Candidal infection, and determine appropriate therapy (14). 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 species were considered pathogenic when isolated from a patient with peritonitis or an abscess after abdominal surgery. If isolated from a polymicrobial culture, the Candida species 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%) group A patients and 19/30 (68%) group B patients. All patients in group A had recurrent perforations necessitating multiple surgical procedures. In contrast, the majority of group B patients underwent a single operation. All patients in group B recovered without antifungal administration. Only 3/19 (16%) recovered with surgical drainage alone. The remainder either recovered with a combination of repeat surgical management and antifungal therapy (n=9) or died from uncontrolled infection (n=6). 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% vs. 3%;p=0.002) (Class III).

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 (15). The primary endpoint was the frequency of and time to intra-abdominal Candida infection. Secondary endpoints included the frequency of intra- and extra-abdominal candidiasis and the
emergence of colonization. Patients with recent abdominal surgery and who had recurrent GI perforations or anastomotic leaks (suspected or confirmed) were eligible. Fluconazole was continued until complete resolution of the intra-abdominal disease, development of Candida infection, or drug-related adverse effect. Routine cultures of blood, urine, intra-abdominal fluid, respiratory tract, skin and soft tissue, and mucous membranes were performed. Infection was defined as the presence of intra-abdominal candidiasis, candidemia, Candida urinary tract infection, or biopsy-proven tissue invasion. Although designed to include 202 patients, enrollment was terminated early secondary to slow recruitment. Forty-three patients were evaluated (23 fluconazole, 20 placebo). The median APACHE II score in both groups was 13. Baseline Candida colonization was present in 44% (10/23) fluconazole patients and 35% (7/20) of placebo patients. All patients received antibiotic therapy. There were no significant differences in baseline characteristics. Candida peritonitis occurred in 4% (1/23) of fluconazole patients and 35% (7/20) of placebo patients (RR 0.12, CI 0.02-0.93, p=0.02). When all infections (intra- and extra-abdominal) were analyzed, there was no significant difference between groups. Patients in the fluconazole group had significantly longer disease-free intervals (p=0.04). There was no difference in mortality, although the study was likely underpowered to detect a difference. In conclusion, fluconazole significantly decreased Candida peritonitis in high-risk GI surgery patients (Class I).

Candiduria
Nassoura et al. performed a two-part study to investigate the role of fluconazole in surgical ICU patients with candiduria (>100,000 CFU/ml) (8). Part I was retrospective and included 27 patients with candiduria. All 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 (200 mg daily). Sixty-three percent of patients in the retrospective analysis developed disseminated infection despite amphotericin B bladder irrigation. Their mean APACHE II score was 13. Of these, 59% had candidemia. Mortality for patients with disseminated infection was 53% (9/17 died of multi-system organ failure and sepsis). No patient in the prospective analysis developed disseminated Candidal infection. Their mean APACHE II score at the time of admission was 12.8. Mortality in this group was 5% (1/20 died of septic complications while on fluconazole) (Class III).

Ang et al. retrospectively identified patients with concomitant candiduria and candidemia in order to identify the characteristics associated with the development of candidemia from a urinary source (16). Of the 26 patients identified, 73% suffered from malignancy, 85% had received at least a one-week course of broad-spectrum antibiotics, and 88% had structural abnormalities of the urinary tract (Class III).

Sobel et al. conducted a prospective, multicenter, placebo-controlled study evaluating the efficacy of fluconazole in patients with asymptomatic or minimally symptomatic candiduria (17). Candiduria was defined as ≥1000 CFU/ml yeast in two consecutive urine cultures. Catheterized patients were eligible only if candiduria persisted following removal or changing of the catheter. Exclusion criteria included urologic obstructive abnormalities, neutropenia, and evidence of fungal infection at an extrarectal site. Treatment consisted of either fluconazole (400 mg loading dose followed by 200 mg/day) or placebo for 14 days. Three hundred and sixteen patients were evaluated, most of which were elderly and had received a recent course of antibiotics. Approximately half were catheterized and diabetic. Candida albicans accounted for most cases of candiduria (50% in fluconazole group and 49% in placebo group). Candida glabrata was isolated in 18% of fluconazole patients and 24% of placebo patients. Following completion of therapy, eradication rates were significantly greater in the fluconazole group (50% vs. 29%, p<0.001). Eradication rates with fluconazole were significantly higher in non-catheterized patients (63% vs. 39%, p=0.004). Mycologic cure occurred in only 20% of those managed with a catheter change alone (Class I).

Voriconazole
Ostrosky-Zeichner et al. published a comprehensive review of the open-label and compassionate use programs using voriconazole as salvage treatment for invasive candidiasis (18). Fifty-two patients demonstrating intolerance to other antifungal agents or with an infection refractory to other antifungal agents were analyzed. The median number of previous antifungal agents used was 2. Fifty-six percent of these patients had previously received amphotericin B and 62% had received fluconazole. The median dose of voriconazole was 400 mg daily, with mean treatment duration of 36 days. Overall, a 56%
response rate was seen. The following response rates were seen for specific Candida species: C. albicans (44%), C. glabrata (38%), C. krusei (70%), C. tropicalis (67%), and other Candida species including C. parapsilosis and C. famata (100%). Five patients had a breakthrough fungal infection despite voriconazole therapy. The most frequent adverse events reported include nausea and vomiting, abnormal liver enzymes, visual disturbances, rash, arrhythmia, and abdominal pain. (Class III)

Caspofungin
Mora-Duarte et al. conducted a double-blind trial comparing the efficacy of caspofungin and amphotericin B for the treatment of primary invasive candidiasis (19). Patients with at least 1 positive candida culture from the blood or other sterile site within the previous 4 days were stratified according to the severity of disease and the presence or absence of neutropenia. Patients with suspected endocarditis, osteomyelitis, or meningitis were excluded. Additionally, patients who received previous antifungal therapy for greater than 2 days with a cumulative dose of amphotericin B > 2 mg/kg, lipid amphotericin B > 10 mg/kg or fluconazole > 1600 mg were not evaluated. Patients randomized to the caspofungin group received 70 mg intravenously on day 1, then 50 mg intravenously daily thereafter. Patients randomized to amphotericin B were dosed based on their neutropenic status. Non-neutropenic patients received amphotericin B at doses between 0.6-0.7 mg/kg/day, while neutropenic patients received amphotericin B at doses between 0.7-1.0 mg/kg/day. Antifungal therapy continued for 14 days after the most recent candida culture. A minimum of 10 days of intravenous therapy was required, after which patients could be switched to oral fluconazole, provided that they were not neutropenic, they were showing signs of clinical improvement, and had negative follow-up cultures for 48 hours. Patients with Candida krusei or Candida glabrata were continued on intravenous therapy.

A total of 224 patients were included in the modified intention-to-treat analysis. One hundred nine patients received caspofungin and 115 patients received conventional amphotericin B. Approximately 60% of patients had received prior antifungal therapy for a maximum of 1 day. The most common candida isolate was C. albicans, which accounted for 36% in the amphotericin B group and 54% in the caspofungin group. Other isolates included C. parapsilosis, C. tropicalis, C. glabrata, and C. krusei. Oral fluconazole was started in 35% of patients receiving amphotericin B and 25% of those receiving caspofungin following 10 days of intravenous therapy. In the modified intent-to-treat analysis, the proportion of patients with a favorable response at the end of intravenous therapy was similar between the caspofungin (73%) and amphotericin B (62%) groups. In the analysis of patients who met the prespecified criteria for evaluation, the percentage of patients with successful outcomes at the end of intravenous therapy was significantly greater for the caspofungin treated patients (81% versus 65%). For C. albicans, the rate of a favorable response was 64% for the caspofungin group and 58% for the amphotericin B group. A total of 5 patients, 3 in the caspofungin group and 2 in the amphotericin B group, had a relapse of candidemia.

Of the patients with candidemia who were included in the modified intention to treat group, 72% in the caspofungin group and 63% in the amphotericin group had a favorable response; however, this difference was not significant. Among the patients with candidemia who met the prespecified criteria for evaluation, 80% in the caspofungin group and 65% in the amphotericin B group had a favorable response, which was statistically significant. There was no significant difference in the response rates between the 2 groups in patients with peritonitis, intra-abdominal abscesses, and multiple sites of infection. The mortality rate among all patients was similar between treatment groups. There were significantly more adverse events in the patients receiving amphotericin B. (Class I)
REFERENCES

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Positive culture for yeast?

No

Yes

Systemic evidence of infection?

No

Yes

2 or more risk factors for fungal infection?

No

Yes

Inadequate response to appropriate antibiotics?

No

Yes

Initiate Fluconazole 800mg x 1 then 400 mg qD*

END

END

Inadequate response to appropriate antibiotics?

No

Yes

Change vascular access lines to new site

END

YES

No

Is fungemia present?

No

Yes

ICS w/ significant CFU on quant culture?

No

Yes

Is source a urinary catheter?

No

Yes

Is surgical debridement indicated?

No

Yes

Surgical debridement / drainage of infection

Change urinary catheter

Antifungal therapy not indicated

Patient with 2 or more risk factors?

No

Yes

Is candida species known?

No

Suspect C. krusei?

No

Suspect Torulopsis glabrata**?

No

Yes

C. krusei?

Yes

No

Reculture patient

Initiate Fluconazole 800mg x 1 then 400 mg qD**

Patient with 2 or more risk factors?

END

YES

No

Reculture patient

Initiate Fluconazole 800mg x 1 then 400 mg qD**

Notes:

ICS = intracutaneous segment

* Enteral Fluconazole should be used when possible. Doses are for normal renal function.

** For patients demonstrating either treatment failure or intolerance, Caspofungin 70 mg IV x 1 then 50 mg IV QD may be used. Not for candiduria. Doses for normal hepatic function.

*** Consider sending isolate for MIC testing.

Risk Factors for Fungal Infection

Critical Illness
Immunosuppressive disease states or drugs
Prolonged broad spectrum antibiotics
Central venous catheter
GI perforation
Peritonitis

Surgical debridement / drainage of infection

Change urinary catheter

Antifungal therapy not indicated

Patient with 2 or more risk factors?

END

YES

No

Reculture patient

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