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Surgical Perspective on Invasive *Candida* Infections

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Abstract. Invasive and disseminated *Candida* infections have become a major source of morbidity and mortality in the modern surgical intensive care unit. The most common risks for invasion and dissemination are the use of antibiotics, central venous lines, total parenteral nutrition, burns, immunosuppression, and other markers for severity of illness (APACHE > 10, ventilatory use for > 48 hours). Data suggest that colonization can be a late predictor of invasive disease in today's critically ill surgical patient and that prophylaxis or early treatment in high risk patients is warranted, particularly before invasive/disseminated disease becomes life-threatening. When advanced disease is present, the diagnosis of invasive or disseminated *Candida* infection is often prompted by clinical suspicion and supported by consistent clinical data; laboratory tests alone lack sufficient sensitivity and specificity to direct therapeutic decision-making. Once the diagnosis of invasive or disseminated *Candida* infection is ascertained, early systemic treatment, along with treatment of localized infection, is as fundamental as with any other serious infectious disease. Reported toxicity and efficacy supports the use of fluconazole for most patients with invasive/disseminated *Candida* infections. For the most critically ill surgical patient amphotericin B remains the treatment of choice. Prophylaxis and early treatment strategies with minimally toxic agents may diminish the need to use more toxic therapy in the most severely ill patients.

Prior to the 1960s, invasive and disseminated fungal infection was a rare diagnosis. The invasive potential of *Candida* was dramatically documented in 1969 when Krause et al. recovered *Candida* from urine and blood following ingestion of the organism into normal-functioning intestine [1]. Autopsy studies during the 1970s proved that *Candida* could infiltrate solid organs without producing clinical organ dysfunction [2, 3]. Today, advances in surgical and critical care management have resulted in the survival of many critically ill surgical patients days beyond the first life-threatening disease or trauma. Such patients are at high risk for fungal colonization and may subsequently suffer invasive or disseminated fungal disease as another threat to life.

The National Nosocomial Infections Surveillance System of the Centers for Disease Control and Prevention (CDC) reports that during the past decade *Candida* has increased in rank from the eighth to the fourth most common nosocomial pathogen isolated in blood, and accounts for 8% to 15% of all hospital-acquired bloodstream infections [4–6]. In surgical patients the incidence has jumped from 2.5/1000 to 5.6/1000 discharges, an increase of 124% [5]. The morbidity and mortality associated with these infections is striking, with the median intensive care unit (ICU)/hospital stay increased by as much as 30 days [7] and death rates of 30% to 80% [6, 8–12].

In response to the high mortality associated with invasive/disseminated *Candida* infection, prophylaxis and early therapy strategies have emerged with the expectation that mobidity and mortality from this infectious disease would decrease. The potential efficacy of such interventions in this critically ill population is controversial [13] but at least warrants continued study. In this review the diagnosis and management of invasive/disseminated *Candida* infection are presented first, followed by a discussion of early therapy and prophylaxis.

Definitions

For this review *colonization* represents simply recovery of an organism at a cultured site regardless of its concentration. *Invasion* is present if the organism has penetrated viable tissue in sufficient numbers to result in a recognized inflammatory response, organisms are visible in pathology specimens, or blood cultures are positive. Dissemination is present when, following invasion at one site, the organism lodges in a distant site(s) where a new invasive focus develops.

Pathogens

Fungi of common clinical significance in the surgical ICU are *Candida* and *Torulopsis* species. *Candida* exists as two forms (dimorphism): yeast and mycelial. With most dimorphic fungi the yeast form is invasive, but for *Candida* it is the mycelial form, a phenomenon known as reverse dimorphism. Both forms of *Candida* have been isolated at autopsy, and the presence of both forms is pathognomonic of invasive infection. *C. albicans* is a commensal organism that colonizes the mucosal tissue of the gastrointestinal and genitourinary tracts of humans. It is the primary fungal pathogen isolated from blood, tissue, and other body fluids. In one autopsy study of 109 fatal pediatric cases, approximately 90% had at least one major organ affected with fungus, but antemortem studies were not predictive of such invasiveness [14]. *C. krusei*, a historically rare *Candida* species, has recently gained clinical importance, as it is now being reported in 1% to 3% of isolates [8,

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15]. *C. krusei* is an important pathogen among neutropenic patients with hematologic malignancies [15]. Virulence and associated mortality parallel that of other *Candida* species. This organism is resistant to fluconazole, a distinction of critical clinical significance for hospitals where *C. krusei* is nosocomial [16].

Torulopsis is often considered to be a member of the genus *Candida*, with the names being interchanged throughout the literature. Unlike *Candida*, *Torulopsis* exists only in the yeast form. *Torulopsis* can be found colonizing mucosal surfaces of the gastrointestinal and genitourinary tracts in humans. *T. glabrata*, also found in the literature as *C. glabrata*, is thought to be less virulent. Surgical and solid tumor patients are most often affected. *T. glabrata* infection is associated with a mortality rate of 50% to 70% [8, 17].

Diagnosis and Management of Invasive/Disseminated Fungal Infection

Diagnosis

The laboratory diagnosis of invasive/disseminated candidiasis is difficult. The initial workup for the surgical patient suspected of having fungal sepsis begins with cultures of sputum, urine, blood, drains, and probably stool and the wound(s). Reliance on blood cultures to document invasion can be misleading. First, *Candida* can be difficult to grow, and concomitant bacterial infection may decrease recovery of *Candida* from blood cultures. Second, only approximately 50% of patients with invasive candidiasis have positive blood cultures [18, 19]. Methods to increase the sensitivity of blood cultures include lysis centrifugation and arterial instead of venous blood sampling. Lysis centrifugation has increased the yield of positive cultures by 30% to 40% and enables quantification of yeast [20]. Sampling the arterial system remains controversial for reasons of access (usually through a catheter) and the potential morbidity associated with multiple arterial punctures.

Further complicating diagnostic distinctions, positive blood cultures do not necessarily indicate dissemination or that the origin of the invasion is cryptic. For instance, a central venous catheter may be the invasive focus, and primary treatment may be removal of the catheter, precluding the need for aggressive systemic therapy.

Positive cultures of urine, peritoneal fluid, and burn wounds are difficult to interpret. All can be colonized, but the presence of *Candida* may indicate invasive disease in the appropriate setting (see below) [10, 21–23].

Serologic tests to mannan and β-1,3-glucan (cell wall components), D-arabinitol (cell membrane metabolite), and enolase (cell cytoplasm) are available with mixed sensitivities and specificities [24–27]. Correlation of dissemination with *Candida* antigen titers has been advocated [28], but routine antibody tests have not proved useful [29, 30].

Histologic examination demonstrating yeast, mycelia, or both, is considered definitive for the diagnosis of invasion. Acquisition of this tissue, however, usually requires an invasive procedure. Some authors include the invasion of wounds [31] as defined by quantitative tissue culture as sufficient evidence to prompt systemic and local therapy.

Table 1. Risk factors for invasive and disseminated fungal infection.[a]

Acute renal failure
Age > 40 years
Second and third degree burns
Antibiotics ≥ 7 days
≥Three antibiotics
Gram-negative sepsis
Acute peritonitis
Intraabdominal abscess
Diabetes mellitus
Cancer
Parenteral nutrition
Multiple organ system trauma
Serum glucose > 200 mg/dl
Severe head injury
Steroids

[a]High risk ≥ 3 risk factors; low risk < 3 risk factors.

Table 2. Diagnostic criteria for disseminated fungal infection.

Definitive criteria
Culture of fungus from tissue (e.g., kidney or lung)
Endophthalmitis
Burn wound invasion
Culture from peritoneal fluid
Likely criteria
Two positive blood cultures at least 24 hours apart, without a central line
Two positive blood cultures with a second obtained >24 hours after removal of a central venous line
Three or more colonized sites

Physical Diagnosis

The physical diagnosis of invasive/disseminated fungal infection is as difficult as using laboratory tests. Most symptoms are nonspecific, but myalgias and characteristic skin lesions are associated with specific *Candida* species [25, 32–34]. Endophthalmitis is present in up to 30% of patients with candidemia. Its presence is widely accepted as a criterion for the diagnosis of disseminated disease [35]. In addition to routine surveillance cultures, serial funduscopic examinations may be helpful so long as the diagnosis of fungal sepsis is being entertained.

Clinical Diagnosis

In keeping with the recognized difficulties establishing a definitive diagnosis of *Candida* invasion/dissemination and the understanding that such infection can be life-threatening, the diagnosis of severe candidiasis is frequently based on the overall clinical status of the patient and a few laboratory aids. As described below (see Risk Factors), recognition of the patient at risk for colonization and subsequent invasion/dissemination is paramount to this clinical diagnosis (Table 1). Once the patient at risk is recognized, diagnostic criteria such as those provided in Table 2 should be sufficient to prompt aggressive therapy [10, 36].

Treatment

Successful treatment of *Candida* infection requires a combination of the surgical principles of drainage and débridement, along with systemic therapy with antifungal agents. In addition, the removal

of infected vascular access catheters and sometimes prosthetics is necessary to cure the infection. Currently amphotericin B and fluconazole are the primary therapeutic agents for the systemic treatment of invasive/disseminated *Candida* infections.

Amphotericin B is active against both *Candida* and *Torulopsis*. Resistance is rare. Amphotericin B is usually administered intravenously but can be given intrathecally or intravesically. A common practice is to give a 1-mg test dose to observe for hypersensitivity reactions, which occur in 20% of patients. Some [37, 38] have opted not to give the test dosage but instead start with the target dose. The target dose and length of treatment based on the data of Solomkin et al. [39] is 0.5 mg/kg/day for 12 to 14 days, although doses of 0.7 mg/kg/day have been recommended. Studies have demonstrated that the blood levels are not influenced by renal or hepatic failure or by hemodialysis [40], although most authors recommend that the dosage be decreased or treatment stopped if renal function continues to deteriorate.

Worsening renal function, hypokalemia, and hypomagnesemia are the primary toxicities, as is occasionally mild anemia. Fever and rigors are common side effects, but this incidence can be decreased with pretreatment (acetaminophen, diphenhydramine, meperidine, or any combination) and, when still problematic, alternate-day treatment. Using the above dosage, renal function is seldom impaired. In fact, when renal impairment is secondary to invasive/disseminated disease, improvement in renal function can parallel resolution of the septic state with amphotericin therapy [39]. Despite its side effects, amphotericin B is still advocated for the treatment of invasive/disseminated *Candida* infection in the *most critically ill* surgical patients.

Clinical use of fluconazole, a less toxic therapy, for invasive/disseminated fungal infection is increasing. Fluconazole is well absorbed from the gastrointestinal tract regardless of the pH, and bioavailability is excellent (>90%) via both oral and intravenous routes [41]. Excellent tissue levels are achieved, and migration across the blood–brain barrier has been demonstrated [41]. Because it is excreted in the urine unchanged, the dose requires adjustment for renal failure. Side effects are rare. Hepatoxicity (elevated transaminase levels) has been reported, and nausea and vomiting are seen occasionally. Drug interactions are similar to those of ketoconazole, including its effects on cyclosporin levels [42].

Fluconazole has fungistatic activity against most species of *Candida* (except *C. krusei*, which is resistant) [16]. *T. glabrata* is reported to be sensitive to fluconazole, but resistance has been recognized [43]. Prospective randomized studies [44, 45] have demonstrated that fluconazole can be used with equal efficacy to, and fewer side effects than, amphotericin in surgical patients. In the Rex et al. study [44] patients in both treatment groups were equally ill (mean APACHE II score 16), and 70% of both groups had undergone previous surgery. Vascular catheters were considered the primary source of candidemia in 70% of these patients, with *Candida* peritonitis seen in only 5%. These patients were randomized to receive either fluconazole 400 mg/day (FLU) or amphotericin B (AB) 0.5 to 0.6 mg/kg/day. There was no significant difference in successful outcomes between treatment groups (70% for FLU vs. 79% for AB), and mortality did not differ between these nonneutropenic groups (33% for FLU vs. 40% for AB). Kujath et al [45] reported on a series of 40 surgical patients with deep-seated fungal infection (determined by biopsy) who were randomized to either fluconazole (400 mg load, 300 mg/day) or amphotericin B (up to 0.5 mg/kg/day) and flucytosine (2.5 g tid) (AB/F). They were equally ill (APACHE 16, fungal risk score 10, fungal infection score 12.5) and had visceral perforation as the most common underlying disease. There was no statistical difference in the eradication of disease (67% for FLU vs. 82% for AB/F) or mortality (30% for FLU vs. 25% for AB/F), but the AB/F arm had a statistically significant shorter median time to elimination of fungi (5.5 days vs. 8.5 days). The primary toxicity related to amphotericin B administration, worsening renal function, was significantly less in both studies with fluconazole.

These studies suggest that fluconazole is adequate therapy for most patients with serious *Candida* infection. Despite this information, it is unclear if the most severely ill patients (e.g., APACHE > 16, multisystem organ failure) suffering from invasive/disseminated disease should receive fluconazole as the initial therapy. On the other hand, a logical strategy of diagnostic/therapeutic or prophylactic intervention with nontoxic agents might prevent the most life-threatening *Candida* infections from developing and avoid the need to provide potentially toxic therapy to the most critically ill surgical patients. The first of these strategies is termed early presumptive therapy (EPT).

Risk Factors and Management of Fungal Colonization (Early Presumptive Therapy)

As stated above, given the difficulty of securing a diagnosis of invasive/disseminated *Candida* infection, it is important for the clinician to know the risk factors for fungal colonization and subsequent invasion/dissemination (Table 1). The most common factors are broad-spectrum antibiotics, indwelling central access catheters, total parenteral nutrition, immunosuppression, burns, and a general measure of severity of illness (APACHE > 10, ventilator use > 48 hours).

Antibiotics

Antibacterial antibiotics lead to suppression of the normal intestinal flora and the overgrowth of *Candida* [31]. Several experimental studies support the concept that members of the indigenous intestinal bacterial flora suppress growth of *Candida* [21, 46, 47], and other data suggest these organisms also inhibit *Candida* adhesion to mucosal cells. Samonis et al. demonstrated prospectively that antibiotics with anaerobic activity or high intestinal concentrations caused a higher and more sustained increase in yeast colonization as detected by stool culture [48]. D'Amelio et al. demonstrated that metronidazole was the only antibiotic in their series that predicted fungal colonization [49]. Thus when bacterial counts decrease secondary to suppression by antibiotics, *Candida* is able to grow in the intestinal lumen and bind to intestinal cells. Both of these processes promote the potential for *Candida* organisms to migrate to other sites [48]. Sometimes this migration results in colonization, sometimes invasion.

In 1974 Stone et al. [21] demonstrated that *Candida* could migrate across an intact gastrointestinal lumen by the mechanism then termed persorption [50], the phenomenon of paracellular or transcellular passage of particles through an intact epithelium. This process is now called translocation. In that study *Candida*, at concentrations of 10^{15} organisms/ml injected into the canine intestinal lumen, migrated across the intestinal membrane and

into the portal vein. Given the canine's lack of previous exposure to fungus, these results were suspect. Therefore the studies were repeated in rhesus monkeys, and jejunal translocation was confirmed.

Whether translocation of bacteria and fungal organisms regularly occurs in humans is debatable. For *Candida* the best evidence that translocation is possible in humans dates back to 1969 when Krause et al. [1], described the onset of symptoms suggestive of septicemia 2 hours after ingestion of a suspension of 10^{12} *Candida* cells into a normal human gastrointestinal tract. Blood and urine cultures were positive. The ingestion of oral nystatin and cathartics provided almost immediate relief.

Critically ill surgical patients are subject to disease and surgical interventions (e.g., intestinal perforations, intestinal surgery, ischemia, bowel obstruction, total parenteral nutrition) that can diminish the normal intestinal barrier to translocation. Because *Candida* in sufficient concentration has been demonstrated to migrate across normal intestinal mucosa, presumably overgrowth of *Candida* would aggravate the tendency for migration when the mucosal barrier is not normal. The recognition that *Candida* is one of the organisms commonly located in the lumen of the proximal gastrointestinal tract in critically ill surgical patients and is part of the flora of late infectious complications in the abdominal cavity as well as elsewhere supports the translocation concept [51].

Central Venous Catheters

The overgrowth of *Candida* in the gastrointestinal tract coincides with colonization of the skin, tracheobronchial tree, bladder, and other sites. Because of skin colonization, any break in the epithelial barrier could act as a portal for invasion. Hence central venous lines and other hardware traversing the epithelium are important risk factors in the development of fungal invasion. Previous concepts of fungal invasion considered the catheter itself and tubing as the primary source of the fungus, which may be the case with *Candida parapsilosis* [52]. For *Candida albicans*, the more current concept is that the patient is the source of the fungus and the catheter is the wick [9, 37].

Total Parenteral Nutrition

Total parenteral nutrition (TPN) is a risk factor in the development of fungal invasion now considered separate and additive to the risk from the central venous catheter. TPN is a highly concentrated glucose mixture combined with electrolytes, trace minerals, protein, and fats. Experimentally, TPN has been shown to reduce complement fixation, inactivate immunoglobulins, and suppress macrophage function [53–56]. The use of TPN instead of enteral feeding has been shown to produce atrophy of intestinal mucosa, possibly secondary to deficient glutamine content [57]. Shou et al. and Alverdy et al. have demonstrated an increase in the frequency of translocation with TPN [58, 59]. Lastly, studies have documented contamination of TPN in fungal epidemics [60].

Immunosuppression

Immunosuppression can result from major surgery, trauma, burns, cancer, bacterial sepsis, hypoperfusion, the use of corticosteroids, chemotherapy, diabetes, and immunosuppressive transplant therapy [9, 61–65]. The immunocompromised state leads to increased risk of invasion by low virulent pathogens such as *Candida* and *Torulopsis*. Superficial infections with *Candida* or *Torulopsis* have been linked with T-cell competence [66]. Patients with chronic mucocutaneous candidiasis are found to have cell-mediated dysfunction but normal function and levels of immunoglobulins and phagocytes [66]. Protection from intestinal colonization has been shown to be T cell-mediated; but once the mucosa is invaded, phagocytic cells become the primary defense [67, 68]. Thus defense against fungal infection requires both T cell immunity (prevention of colonization) and phagocytic immunity (prevention of hematogenous dissemination). Any disease state that suppresses these factors, including major surgical interventions, puts a patient at increased risk for developing disseminated fungal disease.

Burns

The burn patient is an ideal model for susceptibility to *Candida* invasion and dissemination. First, these patients have a loss of mechanical barriers. Not only is the skin barrier lost, but gastrointestinal mucosal atrophy has been correlated with percent body burn [69]. In addition to loss of gut mucosa, patients with more than 25% total body burn usually have an ileus, and hence enteral feeding is sometimes impractical. Second, percent body burn has been correlated with immunosuppression. Studies have demonstrated that burn patients have decreased numbers of CD3, CD4, and CD8 T cells with inversion of the normal CD8/CD4 ratio [61, 70]. Immunoglobulin levels and phagocytic function have been reportedly decreased in burn patients [62]. Interleukin-2 (IL-2) production and receptor affinity are decreased [71]. Other immunosuppressive factors, such as increased complement degradation products and a burn-specific polypeptide, have been measured in burn victims [72]. Finally, these patients are highly susceptible to bacterial invasion; they usually receive at least one course of antibiotics and commonly have indwelling central venous and urinary catheters.

Markers of Illness Severity

The previously discussed risk factors are useful for the development and understanding of the pathophysiology of invasion and are univariately important. It would be useful to have a model that predicted the patients most susceptible to fungal invasion. A previous study [9] stratified the risk of colonization and invasion by grouping patients into high risk ($\geq$ 3 of 15 risk factors, Table 1) and low risk ($<$ 3 factors) groups. In a prospective multivariate analysis, Savino et al. [73] documented three easily measured variables that placed a patient at increased risk: moderate severity of illness (APACHE $>$ 10), ventilator dependence ($>$ 48 hours), and use of multiple antibiotics. Such studies argue that many of the patients residing in the ICU, even those who are not the most severely ill, are at risk for fungal colonization and invasion. In practice, only severity of illness and use of multiple antibiotics have been shown to indicate increased risk of colonization and invasion.

What to Do About Colonization: Concept of Early Presumptive Therapy

As described above, the critically ill surgical patient who is at risk for *Candida* colonization is also at risk for invasive/disseminated disease, which is associated with high morbidity and mortality. However, not every patient who exhibits colonization develops life-threatening infection. The resultant clinical decision-making inquiry would evaluate whether a combination of risk parameters and knowledge of colonization can *select* patients who would benefit from therapy before invasive/disseminated disease develops. This concept of early presumptive therapy (EPT) is illustrated by studies evaluating the treatment of urinary tract *Candida* infection in critically ill surgical patients.

The significance of candiduria is debated. Candiduria is associated with various diseases, including cystitis, ascending renal candidiasis, ureteropelvic fungus balls, and disseminated disease with secondary renal involvement. Stone et al. [21] identified candiduria as being a useful indicator of systemic candidiasis, stating that candidiasis without candiduria is highly unlikely. Dyess et al. [10] and others [7] have shown less sensitivity of candiduria as a marker for candidemia. Hence when the critically ill surgical patient grows 10^5 *Candida* per milliliter of urine, does it represent a local or a systemic disease? Should it be managed with local therapy (amphotericin bladder irrigation) or systemic therapy (systemic amphotericin or fluconazole)?

Nassoura et al. [74] retrospectively evaluated 27 critically ill surgical patients (mean APACHE 13.4) with candiduria ($>$ 100,000 colonies/ml) treated with amphotericin B bladder irrigation. These patients had a dissemination incidence of 63% and sepsis-related mortality 33%. Subsequently, patients with illness this severe who developed candiduria received fluconazole (400 mg load and 200 mg/day); they demonstrated zero incidence of dissemination, and the sepsis-related mortality was reduced to 5%. Candiduria in a critically ill surgical patient can therefore be a marker for invasive/disseminated disease before other markers become positive. Initiating therapy with low doses of a minimally toxic drug may prevent subsequent, more life-threatening and difficult-to-treat illness.

Candiduria is not the only colonization site that prompts EPT. Studies by Slotman et al. [36] and Pittet et al. [75] demonstrated that colonization at diverse sites can be associated with subsequent invasion and should be considered for EPT in the critically ill surgical patient. Within the spectrum of possible sites of *Candida* growth, the use of EPT after finding *Candida* in the peritoneal cavity or in a burn wound deserves more discussion.

Perforations of the intestinal tract, particularly peptic ulcers, may contaminate the abdominal cavity with *Candida* and bacteria. In addition, *Candida* may be recovered from the peritoneal cavity in critically ill surgical patients as part of the syndrome of "tertiary peritonitis," as described by Marshall et al. [51]. Provision of systemic antifungal therapy for growth of *Candida* in the peritoneal cavity should follow guidelines similar to those described for EPT. First and foremost: Is the patient critically ill? If so, the patient's immunocompetence is likely depressed and the organism is more likely to be or to become invasive. Second, are antibacterial antibiotics for intraabdominal organisms being prescribed for this patient? If such is the case, not treating the *Candida* is illogical, as *Candida* can be invasive and cause death, just like bacteria; and treatment of the bacterial infection would likely promote *Candida* growth [22, 23, 31, 76]. Recognition that lack of treatment of the concomitant fungus can become the primary cause of death was well described by Konnes et al. [76].

Should burn wound colonization prompt EPT? Thus far, simple colonization of the burn wound as the only site does not appear to be sufficient evidence for the use of EPT [21]. However, as noted above, (quantitative) biopsy-proved deeper invasion does deserve treatment [31].

Patients at Risk for Fungal Infection (Controversy Regarding Prophylaxis)

The dilemma every surgeon faces is what to do with the surgical patient in the ICU who remains critically ill and is at risk for fungal infection. Previously studies have demonstrated that among severely ill patients who become colonized and are not treated a high percentage develop systemic infection and many die. D'Amelio et al. [48] demonstrated in a prospective study of 72 consecutive surgical ICU patients receiving broad-spectrum antibiotics (mean APACHE 14) that 44% of patients became colonized with fungus. Colonized patients had 47% mortality, whereas noncolonized patients had 20% mortality. Cornwell et al. [77] demonstrated that regardless of the initial site of colonization approximately 50% of these patients would develop systemic infection, and mortality for surgical ICU patients with systemic fungal infection was significantly increased to 36%. One interpretation of these data is that prevention of colonization leads to better outcomes. This conclusion is logical given the available data on the progression from colonization to invasion and possible death, but no study to date has demonstrated a mortality benefit from global prophylaxis.

Slotman and Burchard [78] clearly demonstrated that in critically ill patients systemic prophylaxis with ketaconazole decreased colonization significantly compared to placebo, and none of the treated group developed invasive disease. Prophylaxis against fungal infection is standard therapy in bone marrow transplant wards, and studies have shown its efficacy [79]. It then follows to ask the question: Is there a subset of surgical patients who would benefit from prophylaxis against fungus?

Evidence in favor of judicial use of prophylaxis was demonstrated by Savino et al. [73]. In their prospective randomized trial the routine use of antifungals (fluconazole was not used) was not efficacious, although use in a select population of high risk patients ($>$ 3 risk factors) did reduce colonization and hence may be of benefit. Thus as with EPT, there seems to be a subset of critically ill patients (broad-spectrum antibiotic use, high APACHE score) who would benefit from prophylaxis. The choice of prophylaxis, equally debatable, is outlined below.

Chemotherapy aimed at prophylaxis is either topical or systemic. Nystatin is used in clinical practice today, but because of its toxicity it is not administered parenterally. Its prophylactic use is debated. Nystatin is not absorbed from the gastrointestinal tract, and hence its main efficacy lies in reducing overgrowth. Stone et al. [21, 80] demonstrated that ingestion of nystatin decreased *Candida* sepsis in burn patients, but other studies have demonstrated less favorable results [10, 81]. The dosage of nystatin used for prophylaxis ranges from 10^5 units q4 h to 3×10^6 units q4 h given as swish and swallow.

Ketoconazole is administered orally and requires gastric acidity

for absorption. Reduced serum ketoconazole levels have been reported in patients with natural or iatrogenic achlorhydria [82]. It is highly bound to plasma protein and metabolized in the liver. Side effects include gastrointestinal intolerance, decreased steroidogenesis leading to gynecomastia, and occasionally adrenal insufficiency. Hepatoxicity is also observed, and some advocate weekly transaminase monitoring. Drug interactions include increased levels of warfarin, cyclosporin, phenytoin, digoxin, teferfenidine (cardiac toxicity), oral hypoglycemics, and decreased levels of rifampin and theophylline [42]. For prophylaxis, Slotman and Burchard [78] demonstrated that 200 mg once a day significantly reduced colonization, and that none of the treated group developed fungal sepsis.

Prophylactic use of fluconazole (100–400 mg/day) is common in bone marrow oncology wards. Bodey et al. [83] showed no difference in the fungal infection rate between groups receiving fluconazole 400 mg/day and those receiving amphotericin 0.5 mg/kg three times weekly, although fluconazole was better tolerated. Goodman et al. [79] demonstrated a significant reduction in colonization and systemic illness by *Candida* species in patients receiving fluconazole (400 mg/day) versus those receiving placebo. Although there was no difference in overall mortality between the two groups, the fluconazole-treated arm had significantly fewer deaths attributable to fungal infections. Studies in surgical and trauma patients are ongoing, but recent data in a trauma unit suggest that prophylaxis with fluconazole reduces the incidence of colonization and sepsis [84]. One of the heralded problems with widespread prophylaxis is antimicrobial resistance, and studies have demonstrated that a species shift to *C. krusei* and *T. glabrata* is not insignificant [16, 43].

Conclusions

Epidemiologically, the incidence of candidemia reported in surgical patients is increasing at an alarming rate given the difficulty of diagnosis and the high mortality and morbidity associated with the invasive disease. Autopsy studies reaffirm this concern, as they demonstrate disseminated candidosis without antemortem evidence or clues. The risk factors (Table 1) have not changed, and most surgical patients have two or three upon admission to the ICU. The debate as to when antifungal therapy should be initiated is ongoing. Patients with evidence of disseminated fungal infection can be treated with fluconazole, although the most seriously ill patients should be treated with amphotericin B. Severely ill patients (APACHE $>$ 12, ventilator dependence) may benefit from systemic antifungal agents once they develop colonization. Such EPT treatment should be with fluconazole as it has a low toxicity profile. The benefits from prophylaxis are less clear. However, like EPT patients, high risk patients do benefit in terms of a decreased incidence of colonization and invasive disease with prophylaxis. To date the data support the use of ketaconazole in nonneutropenic surgical patients and fluconazole in neutropenic patients. Therefore the clinician must have a high index of suspicion for the diagnosis of fungal infection, as even moderately ill patients (APACHE $>$ 10) are at risk for invasive, disseminated fungal infection. Thresholds for prophylaxis and treatment intervention must be lowered, as traditional criteria of multiple positive blood cultures or biopsy-positive specimens are probably too late to prevent death and failure of potentially toxic therapy.

Résumé

Les infections invasives et disséminées à *Candida* deviennent une source majeure de morbidité et de mortalité dans les unités de soins intensifs en chirurgie. Les facteurs de risque les plus répandus comprennent les antibiotiques, les cathéters cantraux, la nutrition parentérale totale, les brûlures, l'immunodépression ainsi que d'autres marqueurs de sévérité (APACHE $>$ 10, nécessité de la ventilation mécanique plus de 48 houres). Il ressort de la littérature aujourd'hui que a) la colonisation par le Candida est un facteur prédictif tardif de maladie sévère chez le patient chirurgical grave et b) la prophylaxie ou le traitement précoce constituent une nécessité, surtout avant que l'infection invasive ou disséminée devienne une menace pour le pronostic vital. Lorsqu'on est en présence d'une maladle à un stade avancé, le diagnostic d'une infection à *Candida* est souvent soupçonné cliniquement et confirmé par les données cliniques alors que les tests de laboratoire seuls ne sont ni suffisamment sensibles nl spécifiques pour prendre les décisions correctes. A partiur du moment où le diagnostic d'infection invasive ou disséminée à *Candida* est fait, la mise en route d'un traitement par voie systémique, associé à un traitement local, est fondamentale, comme dans toule autre maladie infectieuse grave. La toxicité et l'efficacité rapportées sont en faveur de l'utilisation de la fluconazole pour la grande majorité de patients ayant une infection invasive et/ou disséminée à *Candida*. Pour la plupart des infections *graves*, l'amphotéricine B reste le traitement de choix. La prophylaxie et le traitement précoce avec des agents à toxicité réduite pourrait diminuer la nécessité d'utiliser des agents plus toxiques chez le patient gravement atteint.

Resumen

Las infecciones invasoras y diseminadas por Candida se han convertido en una causa mayor de morbilidad y mortalidad en las unidades de cuidado intensivo modernas. Los factores más comunes de invasión y diseminación son los antibióticos, las líneas venosas centrales, la nutrición parenteral total, las quemaduras, la inmunosupresión y otros marcadores de gravedad del estado clínico, tales como un índice APACHE $>$ 10 o ventilación mecánica por $>$48 horas. Investigaciones recientes sugieren que la colonización puede ser un predictor tardío de enfermedad invasora en el paciente en estado crítico y que se deben emprender la profilaxis o el tratamiento precoz en los pacientes de alto riesgo, antes de que la enfermedad invasora/diseminada se convierta en un peligro para la vida. Cuando ya existe enfermedad avanzada, con frecuencia el diagnóstico de infección invasora o diseminada por Candida viene a ser insinuado por la sospecha clínica y es apoyado por hallazgos clínicos consistentes, en tanto que las pruebas de laboratorio, de por sí, no poseen suficiente sensibilidad ni especificidad para determinar la toma de decisiones terapéuticas. Una vez establecido el diagnóstico de infección invasora o diseminada por Candida, resulta fundamental, tanto como en cualquiera otra enfermedad infecciosa, iniciar tratamiento de la infección localizada. Los informes sobre toxicidad y eficacia dan apoyo al uso del fluconazol para la mayoría de los pacientes con infecciones invasoras/diseminadas por Candida. La anfotericina B sigue siendo el tratamiento de escogencia para la mayoría de los pacientes en estado crítico. Sin embargo, en la mayor parte de los pacientes en estado crítico, las profilaxis y las

estrategias de tratamiento precoz con agentes de mínima toxicidad pueden llegar a disminuir la necesidad de utilizar terapias más tóxicas.

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