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MEDICAL REVIEWS

Systemic *Candida* Infections

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Over the past two decades, *Candida* species have come to be regarded as important agents of nosocomial infection. In this paper, initially presented as a teaching conference at the Yale University School of Medicine, we summarize recent information pertaining to the epidemiology, diagnosis, and treatment of systemic *Candida* infections.

INTRODUCTION

The past two decades have witnessed a significant change in the epidemiology of nosocomial infections in the United States. Increasing rates of invasive procedures, bone marrow and solid organ transplantation, and use of immunosuppressive agents and broad-spectrum antibiotics have resulted in an increasingly large population of patients with high susceptibility to nosocomial infections. Of note, the rate of fungal infections, primarily caused by *Candida* species, has risen significantly since the early 1980s [1]. These infections are often difficult to diagnose and treat and carry a high burden of morbidity and mortality. We discuss the recent literature pertaining to the changing epidemiology of systemic *Candida* infections in the United States, new diagnostic tests, available antifungal agents, and currently recommended treatment, with an emphasis on candidemia and deep *Candida* infections rather than mucocutaneous manifestations of candidiasis.

EPIDEMIOLOGY

Importance of Candida spp. as nosocomial pathogens

Candida species are the pathogens in an increasing proportion of nosocomial bloodstream infections in the United States. This increase has been noted in hospitals of all sizes, but is particularly striking in large tertiary care institutions. Much of the data documenting this has been collected by the National Nosocomial Infections Surveillance System (NNIS)[b]. This cooperative group of over 100 U.S. hospitals conducts prospective surveillance on nosocomial infections [2]. The participating hospitals are of varying sizes and include both teaching and non-teaching facilities. A uniform definition of nosocomial infection [3] is employed and all such infections were reported to the Centers for Disease Control and Prevention.

The data collected by the NNIS have been analyzed in a number of ways and at several timepoints. All of these analyses indicate an increase in the frequency of fungi as agents of nosocomial infection, with *Candida* spp. being by far the most common agents. Considering all major sites of infection, the proportion of nosocomial infections reported secondary to fungi in 115 of the NNIS hospitals rose from 6.0 percent in 1980 to 10.4 per-

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[b] *Abbreviations:* NNIS, National Nosocomial Infections Surveillance System; 5-FU, 5-fluorouracil; 5-FC, 5-fluorocytosine; cfu, colony-forming units.

cent in 1990 [1]. The overall rate of nosocomial infections secondary to fungi rose from 2.0 to 3.8 infections per 1,000 patient discharges during this period. By site, the largest increases were noted in surgical wound infections (an increase from 1.0 to 3.1 per 10,000 patient discharges), urinary tract infections (9.0 to 20.5 per 10,000 patient discharges) and bloodstream infections (1.0 to 4.5 per 10,000 patient discharges). The majority (78 percent) of these infections were secondary to *Candida* species, predominantly *C. albicans* (approximately 59 percent).

Another study [4] analyzed NNIS data between 1980-1989 to estimate changes in both the rates and microbiology of nosocomially-acquired primary bloodstream infections in 124 hospitals. Hospitals were stratified by size and teaching affiliation. Significant increases in the overall nosocomial bloodstream infection rate were noted in all hospitals studied and ranged from an increase of 279 percent in small nonteaching hospitals to 70 percent in large teaching hospitals. The largest rate increases were noted for four groups of pathogens: coagulase-negative *Staphylococci, Staphylococcus aureus, Enterococci*, and *Candida* spp. For *Candida*, the bloodstream infection rate increased the most in large teaching hospitals (1.61 per 1,000 hospital discharges in 1989, representing a 487 percent increase over 1980).

Candida spp. have supplanted gram-negative rods in terms of frequency of isolation in nosocomial infections (Table 1, [5]). In 1984, *Candida* were the eighth most common pathogen isolated, behind coagulase-negative *Staphylococci, S. aureus*, and several species of gram-negative rods. By 1988, *Candida* spp. rose in frequency to the fourth most common pathogen isolated, surpassing all of the above gram-negative rods.

A recently published twelve-year retrospective study of nosocomial bloodstream infections in a single large tertiary care institution [6] revealed data similar to that obtained by the NNIS. An overall increase in the crude nosocomial infection rate was noted, from 6.7 per 1000 discharges in 1980 to 18.4 per 1000 discharges in 1992. The bulk of this increase was secondary to increases in the rates of *Staphylococci, Enterococci*, and *Candida* spp. The rate of *Candida* bloodstream infection increased twelve-fold during this period.

Table 1: Relative frequencies of bloodstream infection pathogens, 1988 vs. 1984.

Pathogen	Percent of bloodstream infections, 1988	Rank in 1988	Rank in 1984
Coagulase-negative *Staphylococci*	25.5	1	1
S. aureus	15.0	2	2
Enterococci	7.9	3	6
Candida spp.	7.8	4	8
E. coli	6.8	5	3
Enterobacter spp.	5.2	6	7
P. aeruginosa	5.0	7	5
Klebsiella spp.	4.4	8	4

From: Horan et al, [5].

Mortality and risk factors

Candidemia and deep *Candida* infections are associated with a high mortality rate. Most series document a crude mortality rate of sixty to eighty percent [7-9]. The patients

represented in these studies are generally quite ill and have at least one serious comorbid condition (such as leukemia, lymphoma, other malignancy, bacterial sepsis, complicated post-operative course). These underlying conditions could in themselves contribute to a substantial proportion of mortality. One retrospective case-control study [8] attempted to determine the excess mortality attributable to candidemia. In this study 88 candidemic patients were matched with 88 control patients on the basis of age, sex, time in hospital, underlying illness, and major surgical procedure. The crude mortality rate for the candidemic patients was 57 percent, compared with 19 percent for the control patients, with a calculated attributable mortality of 38 percent. Thus, candidemia appears to be responsible for considerable mortality, even after controlling for underlying comorbid illness.

Another recent series of 106 medical and surgical patients [9] with candidemia in a tertiary care hospital attempted to determine host and iatrogenic factors associated with serious *Candida* infections as well as factors predictive of increased mortality. Common factors among the patients revealed the presence of a central venous catheter in 85 percent, use of parenteral hyperalimentation in 61 percent, and prior antibiotic use in 94 percent (62 percent receiving 4 or more antibiotics). Neutropenia was also a common risk factor (29 percent). Patients with sustained candidemia, defined by the authors as positive blood cultures of greater than two days duration, were significantly more likely to die than were those with shorter duration of positive blood cultures (mortality rates of 74 percent vs. 39 percent). Use of central venous catheters, parenteral nutrition, and neutropenia were significantly associated with sustained candidemia. Also, among those with sustained candidemia, infection with a non-albicans species was associated with a higher mortality rate, whereas absence of a malignancy or fatal underlying illness was associated with a lower mortality rate.

PATHOGENESIS

Candida consist of approximately 150 species of oval budding yeasts which are ubiquitous in the environment. Of these, only about 10 species are common pathogens in humans [10]: *C. albicans, C. glabrata* (formerly *Torulopsis glabrata*), *C. guilliermondii, C. parapsilosis, C. tropicalis, C. pseudotropicalis, C. lusitaniae, C. krusei, C. stellatoidea*, and *C. rugosa. C. stellatoidea* is now considered a variant of *C. albicans.*

C. albicans is the most common pathogen, accounting for roughly sixty to seventy-five percent of *Candida* isolates in most series [1, 6, 8]. There is some evidence, however, that this is changing with changing patterns of antifungal administration. In particular, the extensive use of fluconazole appears to select for certain non-albicans species. One institution [11] noted a shift from *C. albicans* as the predominant isolate (87 percent) in 1987 to only 31 percent in 1992 (one year after the introduction of fluconazole). Also noted were proportionate increases in the percentages of *C. glabrata, C. parapsilosis*, and *C. tropicalis* isolates, which were generally less sensitive to fluconazole. Use of fluconazole for prophylaxis in bone marrow transplantation patients [12] was noted to be associated with an approximately twofold higher colonization rate and approximately sevenfold higher infection rate of *C. krusei*, which is natively resistant to fluconazole.

Candida species are normal commensals in the human gut, respiratory, and female genital tracts. The principal defenses against invasive infection are normal bacterial flora, intact integument and, if this is breached, blood and tissue phagocytes [10]. The roles of humoral immunity and T-lymphocytes are less well characterized. Antibodies are made to several *Candida* antigens, but their functional significance is unclear. The importance of T-cell function is suggested by the presence of delayed-type hypersensitivity to *Candida* antigens in most adults with normal immune systems, as well as the increased vulnerability of persons with HIV disease to mucocutaneous *Candida* infections.

The most important risk factors associated with candidemia and deep *Candida* infections are summarized in Table 2. In general, most of these conditions involve either breaching of integument or impaired phagocytic function. Immunosuppression, such as that associated with organ or bone marrow transplantation, is associated with extremely high risk. Some studies suggest a predilection for *C. tropicalis* infections in patients undergoing treatment for leukemia and lymphoma [13, 14], though this has not been as apparent in more recent series [9]. As discussed above, use of broad spectrum antibiotics, central venous catheters, and parenteral hyperalimentation also appear to predispose to candidemia. Parenteral hyperalimentation fluids support growth of *Candida* species by virtue of their high dextrose content. *C. parapsilosis* has been noted to have a particular affinity for such high-dextrose solutions and outbreaks of *C. parapsilosis* fungemia have been traced to contaminated fluids and laboratory equipment used in their preparation [14, 15].

In addition to hematologic malignancies and neutropenia, underlying illnesses associated with an increase in *Candida* infections include human immunodeficiency virus infection, diabetes mellitus, and chronic renal failure. HIV infection definitely does predispose to mucocutaneous candidiasis (oral thrush, esophageal, and vulvovaginal candidiasis), but disseminated candidiasis associated with HIV infection alone is relatively rare [16]. Chronic renal failure predisposes to fungal peritonitis, primarily candidal, in patients with indwelling peritoneal dialysis catheters [17].

Table 2. Risk factors for severe *Candida* infections.

Severe underlying disease
organ transplantation (especially bone marrow)
leukemia, lymphoma
diabetes mellitus
chronic renal failure
Impaired phagocytic function
congenital defects
neutropenia
granulocytopenia
Other conditions and iatrogenic factors
intravenous drug use
central venous catheters
broad spectrum antibiotic use
systemic steroids, immunosuppressive and cytotoxic agents
parenteral hyperalimentation
trauma, burns
abdominal and thoracic surgery

CLINICAL MANIFESTATIONS

Once in the bloodstream, *Candida* produce a clinical picture which is indistinguishable from bacteremia, with fever, leukocytosis, and hypotension, and which may progress to septic shock. In a series of 55 surgical patients with candidemia, 71 percent had a

leukocytosis, 60 percent were febrile, and 29 percent were hypotensive [7]. From the bloodstream the organism can disseminate to multiple organs, producing diffuse microabscesses. The skin, eye, kidney, and brain are most commonly affected, but myocardium, heart valves, joints, and bone may be involved as well [18, 19].

Chronic disseminated candidiasis, also referred to as hepatosplenic candidiasis, is a distinct clinical entity. It occurs primarily in cancer chemotherapy patients who are recovering from neutropenia. Typically patients with this infection have right upper quadrant abdominal pain and are persistently febrile after recovery from neutropenia despite broad spectrum antibiotics [19].

DIAGNOSIS

Most *Candida* species grow well in routine vented or biphasic blood culture bottles [20]. However, severe multiorgan infection can exist in the absence of positive blood cultures. This makes definitive diagnosis of disseminated candidiasis difficult, and often results in delay in the institution of therapy.

Telenti et al. [21] conducted a retrospective review of all cases of *Candida*-positive blood cultures at their institution between 1985 and 1987 (172 episodes in 169 patients). The authors classified each case either as a probable intravascular infection (defined as having intravascular device present, positive peripheral blood cultures before removal of device, catheter tip grew at least 15 colony-forming units (cfu), no other source identified; patients with endocarditis included in this group), or extravascular infection (defined as culture proven extravascular source and either no intravenous device present or tip grew less than 15 colony-forming units). Of these, 39 percent of cases were classified as intravascular, 42 percent as extravascular, and 17 percent as unidentified. Marked differences were observed in the mean colony counts for the intravascular vs. extravascular groups (45 cfu vs. 1 cfu). It is important to note that patients in this study were included on the basis of having a positive peripheral blood culture; therefore each case would be expected to have some number of colony forming units on quantitative culture. The striking feature of these data is the extremely low colony count for nearly all the patients with extravascular infections, as well as a significant number of those with intravascular infections (for 19 of the 172 episodes, 5 or fewer cfu were noted on quantitative culture). These observations suggest that there might be patients with similar infections and negative blood cultures. This possibility is supported by the observations of Berenguer et al. [22]. In a retrospective review of 67 cases of autopsy-proven single-organ and multiorgan disseminated candidiasis, these authors found that only 28 percent of single-organ cases and 58 percent of multiorgan cases had any positive blood cultures, even though the median number of blood cultures was 11 in the single-organ group and 17 in the disseminated group.

The unreliability of culture-based diagnosis has led to substantial efforts to develop other diagnostic methods. These have recently been reviewed elsewhere [23]. Numerous serologic assays have been developed which are designed to detect circulating *Candida* antigens. These include the cell wall polysaccharide mannan, a 48 kD cytoplasmic glycoprotein antigen, and a heat-labile glycoprotein antigen. Another approach involves detection of sugar alcohol metabolites such as D-arabinitol by gas chromatography. Also, a polymerase chain reaction assay was recently developed which detects conserved portions of the *Candida* actin gene [24]. Other assays have been designed which detect antibodies to major cytoplasmic protein antigens. However, no serologic or polymerase chain reaction assay to date has been found to have sufficient sensitivity and specificity. Therefore none of these tests has yet been developed for routine clinical use. Therefore, the decision to treat patients for candidemia and/or disseminated candidiasis rests in large part upon maintaining a high degree of suspicion, particularly in the susceptible host with one or

more risk factors, and often must be undertaken empirically, without confirmatory data from cultures or other tests.

TREATMENT

The currently available antifungal agents most often used to treat patients for documented candidemia and/or disseminated candidiasis include amphotericin B, fluconazole, and 5-fluorocytosine. Of these, amphotericin B is the oldest, and although it has the greatest potential toxicity, it also has the advantage of being the most well-known agent in terms of efficacy in serious *Candida* infections.

Amphotericin B is a lipophilic polyene first isolated in 1956 from *Streptomyces nodosus*. It acts by binding to ergosterol, a steroid crucial to fungal cell wall integrity, causing leakage of cellular contents and cell death. Conventional amphotericin B consists of the drug complexed to sodium deoxycholate in order to improve water solubility. It is available only in intravenous formulation for systemic use, as it is poorly absorbed though the gastrointestinal tract. Cerebrospinal fluid penetration is poor [25, 26]. Amphotericin B has a number of important adverse effects, the most common of which are nephrotoxicity (secondary to renal vascular spasm, proximal and distal tubular damage, and renal tubular acidosis) and anemia (secondary to direct suppression of erythropoesis and sometimes thrombopoesis) [27]. Most species of *Candida* are susceptible, but both primary and secondary resistance are seen in *C. lusitaniae* and occasionally in other *Candida* species [28].

Lipid-associated amphotericin B preparations include liposomal amphotericin B, amphotericin B colloidal dispersion, and amphotericin B lipid-complex. Rather than deoxycholate, the lipid-associated preparations contain amphotericin B incorporated into liposomes, complexed with cholesteryl sulfate, or with dimyristoyl phosphatidylcholine and dimyristoyl phosphatidylglycerol. These agents have a wider therapeutic index than conventional amphotericin B, allowing administration of higher cumulative doses with minimum renal toxicity [29-32]. In addition, these agents are preferentially taken up by the reticuloendothelial cells of the liver and spleen, offering a theoretical advantage in the treatment of hepatosplenic canddiasis. Amphotericin B lipid complex, with dimyristoyl phosphatidylcholine and dimyristoyl phosphatidylglycerol, was recently licensed for use in the United States.

5-Fluorocytosine (5-FC) or flucytosine is a water-soluble pyrimidine. It is converted to 5-fluorouracil (5-FU) by the enzyme cytosine deaminase in susceptible fungi. 5-FU in turn is converted into 5-fluoro-2'-deoxyuridylic acid (FdUMP), which inhibits thymidylate synthtase and therefore inhibits DNA synthesis. Cytosine deaminase is not present in human cells; therefore the conversion of 5-FC to 5-FU is confined to susceptible fungi [33]. It is absorbed well orally and penetrates the cerebrospinal fluid well. Although the majority of *Candida* species are initially susceptible, resistance develops readily; therefore flucytosine cannot be used as a single agent. It is used primarily in combination with amphotericin B in serious candidal and cryptococcal infections which fail to respond to amphotericin B alone. However, no evidence currently exists to suggest that the addition of flucytosine provides any therapeutic advantage over amphotericin alone in the treatment of serious *Candida* infections. The combination of the two can in fact be quite harmful, as both may cause bone marrow suppression [25]. 5-FU has been noted to be present in human serum after the administration of 5-FC, possibly secondary to conversion by intestinal microflora followed by gut reabsorbtion, and this is one mechanism that has been put forth for the myelosuppressive effect of the drug [34]. However, a study of 5-FC toxicity in patients with cryptococcal meningitis found that peak 5-FU levels were not predictive of toxicity [35].

Fluconazole is a water soluble triazole which was introduced in 1991. It selectively inhibits the fungal cytochrome P-450 enzymes which catalyze the conversion of lanosterol to ergosterol. Oral bioavailability is 85-90 percent, and CSF penetration is 80 percent in the presence of inflamed meninges [36]. It has a broad spectrum of activity including most *Candida* species, but *C. krusei* is resistant, as well as *Aspergillus* species.

A comparison of the toxicities and adverse effects of amphotericin B and fluconazole is shown in Table 3. With the exception of hepatic necrosis, which is rare, the adverse effects of fluconazole are relatively minor compared with those of amphotericin B. Also, the most common adverse effects of fluconazole (nausea, abdominal pain and headache) occur with fairly low frequency (less than 2.5 percent) [37]. This contrasts with the frequency of nephrotoxicity (nearly 100 percent) and hematologic toxicity (approximately 75 percent) observed with amphotericin B [27].

Table 3. Adverse effects of amphotericin B and fluconazole.

Amphotericin B	Fluconazole
thrombophlebitis	nausea, vomiting, abdominal pain
chills, fever, aches	rash (rarely exfoliative)
nausea/vomiting	headache
hypotension	elevated liver function tests
nephrotoxicity	hepatic necrosis (rare)
hypokalemia	
hypomagnesemia	
suppression of erythro- and thrombopoesis	

The more favorable toxicity profile of fluconazole makes it an attractive alternative agent to amphotericin B. There are numerous reports in the literature which describe the successful use of fluconazole in the treatment of oropharyngeal candidiasis, as well as deep-seated *Candida* infection, including endocarditis [38], endophthalmitis [39], osteomyelitis [40], and prosthetic joint infections [41]. However, there is a paucity of studies which directly compare the efficacy of fluconazole with that of amphotericin B. Amphotericin B therefore remains the treatment of choice for most sorts of serious *Candida* infection.

One notable exception is in the treatment of candidemia in non-neutropenic patients. A recent randomized trial [42] included 206 patients with culture-documented candidemia without neutropenia or major immunodeficiency (patients with hematologic malignancies, acquired immunodeficiency syndrome, and organ transplantation were excluded) and who had not received greater than 0.6 mg/kg of amphotericin B or 400 mg of fluconazole previously. All had fever, hypotension, or other signs of infection. Patients were randomly assigned to receive either 0.5-0.6 mg/kg/day of amphotericin B or 400 mg/day of fluconazole. Therapy continued for 14 days after the resolution of clinical signs or 14 days after the last positive blood culture, whichever period was longer. Therapy with fluconazole was discontinued if the serum alkaline phosphatase rose to greater than 1.5 times normal or baseline, or if serum transaminases exceeded three times normal or baseline; amphotericin B was discontinued if serum creatinine became greater than 3.5 mg/dl. Patients in either treatment group received approximately the same duration of therapy (mean 17 days for fluconazole and 18 days for amphotericin B). Treatment was judged to be successful in 79 percent of patients in the amphotericin B group and 70 percent of

patients in the fluconazole group; the difference in success rates was not statistically significant. However, rates of adverse effects were significantly higher for amphotericin B than fluconazole. Amphotericin B caused renal failure in 37 percent of 103 patients and hypokalemia in 10 percent, while the frequency of both of these effects was only 2 percent among the 103 patients in the fluconazole group. The frequency of elevated liver function tests, on the other hand, was 14 percent in the fluconazole group (not statistically significant) compared with 10 percent in the amphotericin B group.

This study offers evidence for the promise of fluconazole as an effective, safe therapeutic agent for the treatment of systemic *Candida* infections in non-neutropenic patients. It has important limitations, however, which must be considered. First, the study population was very carefully selected, excluding patients with the most common immunodeficiency states which predispose to serious *Candida* infections. It was not specified whether any patients were on systemic steroid therapy, so it is unclear whether fluconazole would be equally effective to amphotericin B in patients taking such agents. Also, it is important to note that the majority of infections in this study were caused by to C. *albicans*, and that other species were not represented in sufficiently large numbers to allow for detection of differences in the relative efficacy of the two antifungal agents.

The currently recommended first-line therapy for candidemia and disseminated *Candida* infections in neutropenic and otherwise immunocompromised hosts is therefore still amphotericin B, at a dose of 0.5-0.7 mg/kg/day, to be continued until fourteen days after resolution of clinical symptoms and signs or after the last positive blood culture. In non-neutropenic, non-immunosuppressed patients, fluconazole may be used as a first-line agent, with the duration of therapy determined on the same basis. Fluconazole may also be used as a second line agent in immunosuppressed patients who are unable to tolerate the adverse effects of amphotericin B. Any intravascular catheters should be removed and completely changed if possible, as leaving catheters in prolongs the duration of candidemia [43]. Chronic disseminated or hepatosplenic candidiasis responds poorly to conventional amphotericin B therapy [44, 45], but fluconazole is effective and is therefore the first-line therapy for this infection [46-49]. Liposomal amphotericin B has also been found to be effective in chronic disseminated candidiasis [50].

SUMMARY

Systemic *Candida* infections pose many and increasingly frequent challenges in terms of diagnosis and treatment. Timely institution of treatment for these potentially life-threatening infections relies upon maintaining a high degree of clinical suspicion in patients with one or more risk factors, particularly those who remain ill or febrile despite broad spectrum antibacterial agents. Blood cultures are not a sensitive means of detecting candidemia and disseminated candidiasis, and therefore negative blood cultures should not preclude empiric therapy for the at-risk patient in the appropriate clinical situation. Finally, although the toxicity of amphotericin B is problematic, it is still considered the first-line therapy for most systemic candidal infections, with two exceptions being candidemia in non-immunocompromised hosts and chronic disseminated candidiasis.

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