Deep *Candida* infections in the neutropenic and non-neutropenic host: an ISHAM symposium

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A symposium was held on May 8, 2000 to discuss the management of deep infections with *Candida* species. Among the findings discussed were the following. Candiduria is most often benign, though it occurs in patients with serious underlying diseases. *Candida* species are now the fourth most common cause of nosocomial bloodstream infections, usually arising from an intravenous catheter. *Candida albicans* represents only 50–60% of the isolates. There has been no change in the frequency of fluconazole resistance in *C. albicans* but some of the other species now being isolated from blood are constitutively more resistant to this drug. Nevertheless, for most non-neutropenic patients with candidemia, fluconazole is a reasonable choice for initial therapy. In the neutropenic patient, candidemia is now uncommon. Deep candida infections in neutropenic patients are usually being treated empirically with an amphotericin B formulation. Hepatosplenic candidiasis is usually detected only after recovery from neutropenia but can be suspected by imaging techniques. Improved diagnostic techniques for deep candidiasis in the neutropenic patient remain a critical requirement.

**Keywords** *Candida*, candidemia, candidiasis, candiduria

**Introduction**

Problems in the management of candidiasis are compounded by the difficulty in distinguishing colonization from infection, and superficial from deep infection. For example, isolation of *Candida* from the vagina or mouth is so common in uninfected patients that a positive culture from either site can support a diagnosis of superficial candidiasis, but is not diagnostic in and of itself. Contamination of bronchoalveolar lavage and endotracheal tube aspirates with oral *Candida* is also common, particularly in antibiotic-treated patients, so that cultures or smears from these sites do not indicate *Candida* pneumonia. The significance of isolating *Candida* from the urine is more problematic. The culture result can represent any one of a spectrum of conditions, including contamination of the labia or foreskin, asymptomatic infection of a bladder containing a Foley catheter, or pyonephrosis. The long-heralded utility of a positive urine culture as a harbinger of hematogenous candidiasis is more myth...
than reality. What, then, to do with a positive urine culture? If the laboratory only cultures a 1-μl loopful of urine, a common practice, Candida will only be detected if there are 1000 colonies ml⁻¹. This would appear to be a lot of Candida for simple contamination. In the ISHAM symposium summarized in this paper, Dr Kauffman attempts to determine the significance of candiduria. As the paper points out, candiduria is usually benign. Candidemia is present in only one of a hundred patients and, even then, does not necessarily originate from the urinary tract.

Patients found to have Candida in blood cultures usually have serious comorbid conditions, and discerning the burden of illness due to candidemia is often problematic. Dr Sobel reviews the epidemiology of candidemia over the past decade, noting that candidemia is a marker for patients with other serious medical problems. Although Candida albicans was at one time the major species isolated, only half the isolates are now found to be this species. Among the other interesting observations reported, C. parapsilosis is particularly likely to originate from a vascular catheter and has a better prognosis than candidemia from C. albicans. The problem of managing deep candidiasis in the nonneutropenic patients is summarized by Dr Rex. Guidance is given about the necessity of removing intravascular catheters and choice of empirical or specific therapy. The final part of the symposium concerns the management of empirical and specific therapy of deep candidiasis in the neutropenic patient. Drs Girmenia and Menichetti discuss the lack of sensitive and specific diagnostic tests and the necessity of empirical treatment.

A ‘state of the art’ symposium such as this does not provide simple answers for complex questions. The intent, rather, is to review and evaluate the available information to provide the best understanding and guidance possible for the clinician.

Candiduria

Candiduria is an increasingly common finding in hospitalized patients [1,2]. The majority of patients with candiduria are asymptomatic. According to some authorities, candiduria is a marker for hematogenous seeding to the kidneys. In the vast majority of patients, however, candiduria most likely reflects colonization or infection of the lower urinary tract or the collecting system of the kidneys. Unfortunately, colonization versus infection, lower tract versus upper tract involvement, and hematogenous versus ascending infections are very difficult to differentiate clinically.

A prospective surveillance study of 861 hospitalized adults from 10 medical centers followed patients with candiduria for a maximum of 10 weeks or until discharge from the hospital [3]. Candiduria was defined as > 1000 yeast colonies ml⁻¹. Only 94 of 861 patients (11%) with funguria had no underlying illness. Urinary drainage devices, mostly chronic indwelling urethral catheters, were present in 83% of patients. Most patients with funguria were asymptomatic; only 4% of patients had symptoms suggesting a urinary tract infection. Pyuria (> 5 white blood cells per high power field [WBC HPF⁻¹]) was noted in 55% of patients, and 20% had > 50 WBC HPF⁻¹. However, pyuria was not predictive of infection and could not be correlated with outcome. C. albicans was the prominent species isolated (52%); C. glabrata was found in 16%, and C. tropicalis in 8%. It should be noted that 21% of isolates were not identified to species.

Of the 288 patients in whom clearance of funguria was documented, 117 (41%) received no treatment. In an additional 14%, funguria cleared with catheter removal alone. For those patients who received either fluconazole or amphotericin B bladder irrigation, 45% and 54%, respectively, cleared the yeast from their urine. Candidemia was a rare event in this population; only seven patients (1.3%) developed candidemia. Of the 530 patients who had outcomes documented, 105 (19.8%) died. Thus, candiduria appears to be a marker for poor outcomes, presumably related to the multiple serious underlying illnesses and advanced age of this population.

In addition to the historical data about candiduria collected for the above study, the effect of fluconazole has been evaluated in a prospective, randomized, placebo-controlled trial in patients who had asymptomatic or minimally symptomatic candiduria [4]. Patients had to have at least two consecutive urine cultures with at least 1000 Candida colonies ml⁻¹. Patients with fever > 37.8 °C, serum creatinine > 3.5 mg dl⁻¹ or urinary tract obstruction were excluded. Fluconazole was assigned to 159 patients and placebo to 157. By an intent-to-treat analysis, 50% of patients receiving fluconazole and 29% of those receiving placebo had eradication of yeast from urine. For those patients who completed the entire 14 day course of fluconazole, funguria was eradicated in 78% of noncatheterized patients, but only 52% of catheterized patients. No patient developed candidemia, whether given fluconazole or placebo.

Taken together, these studies have shown the benign nature of candiduria in most patients. Removal of the catheter alone will be expected to lead to fungal eradication in as many as 40% of patients. When treatment is deemed necessary (and neither of these studies assessed
the appropriateness of the decision to treat with an antifungal agent) fluconazole is an effective agent.

**Bloodstream infections due to Candida species (1990–1999)**

Bloodstream infections (BSI) due to Candida species were an infrequent event during the 1960s and 1970s. During the 1980s, however, it became apparent that candidemia was occurring at an increased frequency [5]. This epidemiological phenomenon was initially recognized predominately in teaching hospitals and large tertiary care referral hospitals. Nevertheless it soon became evident that the increase was of 21 to 487% [6,7]. The increase was the consequence of numerous factors, primarily the survival of the host with severe, underlying, often fulminating and inevitably fatal underlying disease. Early factors that were recognized as predisposing to candidemia included prolonged neutropenia, intravenous catheters, and parenteral hyperalimentation [6,8]. By the end of the 1980s, nosocomial BSI caused by Candida species constituted 5–10% of all nosocomial bloodstream infections.

Within each medical center, high risk areas were recognized as having a higher incidence of candidemia. This included the neonatal, medical and surgical intensive care units (ICU), transplant units and oncology units. Risk factors in the neonatal ICU were primarily a function of the use of intravenous catheters and were seen predominately, but not exclusively, in low birth weight premature neonates [9]. In the surgical ICU, a high prevalence was seen in burn units as well as in the elderly, following colonic and pancreatic surgery. Risk factors identified in the medical ICU included central venous lines, total parental alimentation, and underlying gastrointestinal diseases. Nosocomial candidiasis was initially evident in the bone marrow transplant unit but later in patients following solid organ transplantation, especially liver and pancreas recipients. The candidemia rate in these tertiary care centers was approximately 10 times higher in the ICU as compared to the general medical units [7].

In the early 1990s, the National Nosocomial Infection Survey (NNIS) conducted by the Centers for Disease Control and Prevention, was undertaken to monitor hospital acquired infections and determined that Candida was the fourth most common organism responsible for bloodstream infections [7].

There have been several investigators who have monitored systemic infections during the 1990s [10–15]. In all of these studies, *C. albicans* represented approximately 50–60% of the overall hospital isolates that were responsible for candidemia. Although the second most common species was *C. tropicalis* in the 1970s and early 1980s [5], there has been a progressive decline in *C. tropicalis* fungemias, particularly during the 1990s [7]. *C. glabrata* has emerged in its place as a major hospital pathogen, although in specific units such as the neonatal ICU and in other pediatric units *C. parapsilosis* has competed with *C. glabrata* for second place. *C. krusei*, which is intrinsically resistant to fluconazole, fortunately causes invariably less than 5% of fungemias and in some hospitals less than 1% [11]. There appear to be marked geographic differences in its occurrence.

There are many nosocomial factors, other than fluconazole use, that may explain the increase risk of BSI due to non-*C. albicans* Candida. First, because of the reduced virulence of non-*C. albicans* Candida, this phenomenon reflects a sicker hospitalized patient at risk of candidemia. In particular, during the 1990s patients received more intensive chemotherapy, permitting the less virulent *Candida* species to invade. Among the species to have increased in frequency has been *C. parapsilosis*, predominantly seen in premature infants receiving total parenteral nutrition via a central venous catheter [9].

The availability of new molecular tools to type *Candida* strains within a species level has enhanced our knowledge of epidemiological trends. A variety of techniques have been used, including DNA hybridization of genomic digests, karyotyping, restriction fragment length polymorphisms and/or random amplified polymorphic DNA (RAPD). These methods tend to agree that each patient maintains their own unique strain [16]. Bloodstream invasion tends to originate from the patient’s own strain.

The crude or overall mortality of nosocomial candidemia is at least 40%, ranging 30–70%, depending upon the underlying disease [6]. The single most important risk factor for death in cancer patients with candidemia is the underlying performance status of the patient [6,17].

The susceptibility to bloodstream isolates of *Candida* to antifungals, both azoles and polyenes, has been closely monitored during the 1990s. Studies of large numbers of bloodstream isolates of *C. albicans* have failed to show a change in susceptibility or progressive resistance to either polyenes or azoles. Thus,azole resistance among *C. albicans* strains varies 1–2% [16]. Comparison of isolates from a variety of diverse geographic sites have similarly failed to show any progressive change in *C. albicans* susceptibility to the aforementioned antifungals.

This observation is in stark contrast to the observation of the progressive decrease in susceptibility of *C. albicans* isolates from acquired immune deficiency syndrome (AIDS) patients with chronic and intractable oropharyn-
geal candidiasis [18]. Overall,azole susceptibility of non-\(C. \text{ albicans}\) \(Candida\) bloodstream isolates is significantly reduced when compared to \(C. \text{ albicans}\). Nevertheless, careful monitoring has once more failed to show increased fluconazole and other azole resistance among \(Candida\) isolates regardless of species and including \(C. \text{ glabrata}\). The study of isolates obtained during 1997 to 1999 failed to show any significant change [16]. Long term monitoring of drug susceptibility remains essential.

### Treatment in non-neutropenic patients

Treatment of invasive candidiasis in the non-neutropenic patient remains an area of intensive study. Two broad areas of current concern can be identified.

Making a convincing diagnosis of invasive candidiasis is a prerequisite for any meaningful study, but is surprisingly difficult. The diagnosis is straightforward if the patient presents with fever and growth of \(Candida\) spp. from a sterile site (e.g., the blood). However, this situation is the exception. Rather, the clinician is far more often faced with a febrile ICU patient where (i) other investigations do not offer an explanation for the fever and (ii) cultures of a non-sterile site (e.g., tracheal aspirate) yield \(Candida\). While such findings are now understood to increase the likelihood of developing invasive candidiasis [19,20], these findings alone do not make a convincing diagnosis. Non-culture based detection systems are not yet available.

Therapy of invasive candidiasis has recently been reviewed in detail, and guidelines for therapy have been proposed by the Infectious Diseases Society of America. In the non-neutropenic patients, fluconazole and amphotericin B are generally found to be similarly effective. Amphotericin B is usually preferred in patients who are infected with \(C. \text{ glabrata}\) (although high doses of fluconazole may be suitable), \(C. \text{ krusei}\), or \(C. \text{ lusitaniae}\) (this species may rapidly become amphotericin B-resistant during therapy [21]), and in patients who are unstable or who have previously received an azole antifungal [22].

In broad terms, intravascular catheters have been closely linked to the development and propagation of candidemia [9,23–25]. Prompt catheter removal has been said to shorten the duration of subsequent candidemia [25] and to reduce mortality [24]. However, close inspection of the data shows that catheter management has never been subjected to randomized analysis, and that patients for whom catheter exchange is avoided are often more severely ill [25].

An excellent example of this problem is the recent report by Anaissie et al. [26] of their experience with candidemia in a series of 479 consecutive cancer patients. Of these patients, 366 had a central venous catheter in place at the time the candidemia was detected and lived long enough to be treated with an antifungal agent. A preliminary crude analysis found that failure to exchange the catheter was associated with a 43% failure rate, which fell to 24% if the catheter was removed \((P < 0.001)\). However, this univariate analysis is severely biased in that the ‘no exchange’ group was more likely to be neutropenic \((54\% \text{ vs. } 27\%, P < 0.001)\) and had a higher APACHE III [27] score \((53 \pm 2 \text{ vs. } 45 \pm 2; P = 0.002)\). When the data were subjected to a multivariate analysis, APACHE III score, clinical evidence of visceral spread, and becoming or remaining neutropenic were all found to be powerful prognostic factors \((P < 0.001 \text{ for each, independently of the others})\). On the other hand, catheter exchange (whether defined to include or exclude exchanges performed in situ over a guidewire) had a much reduced significance \((P = 0.02–0.09)\).

These data suggest that the catheter is less relevant in this patient population. Therefore, if the catheter is not the source, then what is? Approximately 15% of patients with candidemia will have another clearly defined source (e.g., urinary or wound) [12]. However, in neutropenic patients the gut may be a significant alternative source [26,28,29]. However, making such a diagnosis ante mortem is difficult.

In short, it is difficult to know in an individual patient if the catheter must be exchanged. Integrating all data, factors favoring the catheter as a source would appear to be lack of neutropenia, presence of \(C. \text{ parapsilosis}\) in the blood, and recent hyperalimentation. Factors favoring some other source would include recent chemotherapy and neutropenia.

Lesions limited to the retina appear to respond to both amphotericin B and fluconazole [30]. The majority of published results report the use of amphotericin B which, despite its relatively poor ocular penetration, has been quite effective in anecdotal series [31]; lesions that extend into the vitreous appear to benefit from vitrectomy [32]. In addition to reducing the local fungal burden, this also permits intraocular delivery of drug.

As with the idea of empirical therapy, prophylaxis for invasive candidiasis in the non-neutropenic patient is an intriguing but problematic concept. A large \((n \sim 200)\) study of patients with ICU stays of at least 3 days who were randomized to receive fluconazole \((100 \text{ mg day}^{-1})\) versus placebo has been presented in abstract form [33]. Although it showed a trend towards reduction of serious \(Candida\) infections \((7/101 \text{ (7%) vs. } 3/103 \text{ (3%)}; P = 0.2)\), the sample size was too small for such an infrequent event and the absolute reduction in infections was only about 3%.
The key for future studies is to remember this lesson and look for similar high-risk target groups. Recent studies suggest that this should be possible with liver transplant recipients [34]. Careful integration of available data may permit this for other patient groups as well.

Treatment in neutropenic patients

Invasive candidiasis in neutropenic patients continues to be associated with a considerable morbidity and mortality. Clinical and laboratory diagnosis of deep Candida infections is neither sensitive nor specific in the early phases of infection. Consequently, the majority of patients are treated empirically. Heavy colonization of the patient with Candida krusei infections is neither sensitive nor specific in the early phases of infection. Consequently, the majority of patients are treated empirically.

Identification of the Candida species isolated from blood assists in the management. The high affinity for intravascular catheters and the low virulence observed in most C. parapsilosis strains lead to a high suspicion of catheter-related infection when this species is isolated from blood [36]. Conversely, a septicemia caused by a highly pathogenic species, such as C. tropicalis and C. krusei, is more likely associated with deep tissue infection [37]. A diagnostic test to distinguish candidemia arising from a catheter from that arising from deep tissue would be highly desirable, but no such test is available. Catheter tip cultures have been disappointing. In a retrospective pilot study, detection of Candida mannanprotein in blood was less common in candidemia thought to originate from a catheter than from other sites, suggesting that such a test deserves further study [38,39].

Hepatosplenic candidiasis originates during neutropenia and is initially manifested only as fever and abnormal liver enzyme levels. Fever persists after recovery from neutropenia, at which time imaging studies show several enlarging lesions within the liver and/or spleen [40]. Response of the fever and shrinkage of lesions during antifungal therapy is often quite slow. Detection of Candida mannanproteinemia was uncommon in the early stages of focal hepatosplenic candidiasis in a recent preliminary study in our institution (unpublished data). Most patients with proven or probable hepatosplenic candidiasis had undetectable antigen in repeated serum samples.

In conclusion, invasive candidiasis in neutropenic patients is difficult to diagnose. Signs and symptoms are usually non-specific. Culture techniques lack sensitivity and biopsy is often hazardous because of thrombocytopenia or other clotting disorders. Empirical therapy, unfortunately, remains the most common strategy.

Contributors

The contributors to this symposium were: C. A. Kauffman, Candiduria; J. H. Rex, Treatment in non-neutropenic patients; J. D. Sobel, Epidemiology of nosocomial candidiasis: bloodstream infections due to Candida species (1990–1999); C. Girmenia & F. Menichetti, Treatment in neutropenic patients. The co-convenors were I. N. Tiraboschi and J. E. Bennett.

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