

INVASIVE CANDIDIASIS

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Abstract: Invasive candidiasis is of particular concern for many reasons, including the increasing incidence among hospitalized patients, increasing isolation of nonalbicans species, the lack of suggestive specific signs and symptoms, relatively insensitive diagnostic modalities, the complexity of the patients' underlying conditions and the high mortality, especially when prompt antifungal treatment is not administered. Use of rapid diagnostic methods with identification to the species level and standardized in vitro susceptibility testing along with development of risk stratification strategies to guide antifungal therapy and reduce candidemia-related mortality may be the modalities to counter this threat.

INTRODUCTION

Invasive mycoses are life-threatening opportunistic infections and have emerged as a major cause of morbidity and mortality in hospitalized patients. *Candida* is the most common cause of invasive fungal infections, accounting for 70% to 90% of all invasive mycoses¹. Among the causes of bloodstream infection, *Candida* ranks fourth in the United States and seventh in Europe^{2,3}. In 2008, *Candida* was the third most common organism causing blood stream infections among ICU patients at Sir Ganga Ram Hospital, New Delhi.⁴ Rapid initiation of appropriate antifungal therapy is essential for the control of invasive *Candida* infections and has been shown to reduce mortality as part of appropriate therapy⁵.

The term "Invasive Candidiasis" is equivalent to "Disseminated Candidiasis", "Systemic Candidiasis," and "Hematogenous Candidiasis". "Invasive candidiasis" (IC) encompasses a wide variety of severe and invasive disorders that include candidemia, disseminated candidiasis, endocarditis, meningitis, endophthalmitis, and other deep organ involvement. There are three major components to the pathogenesis of IC (1) increased fungal burden or colonization, typically resulting from the use of broad spectrum antimicrobial agents; (2) breakdown of normal mucosal and skin barriers as a result of the use of chronic indwelling intravascular devices, recent surgery or trauma, and severe mucositis associated with cytotoxic chemotherapy and radiation; and (3) immune dysfunction (eg, neutropenia) that leads to dissemination and proliferation in deep tissues. Virtually all patients who have IC have one or more identifiable risk factors for IC (Table 1)⁶.

Table 1: Risk factors for development of invasive Candidiasis

1. Length of stay in the ICU (incidence of IC rises rapidly after 7 to 10 days).
2. Use of central venous catheters.
3. Use of broad-spectrum antimicrobial agents.
4. Parenteral nutrition.
5. Development of acute renal insufficiency, hemodialysis (acute or chronic).
6. Severe pancreatitis.
7. Diabetes mellitus.
8. Neutropenia.
9. Gastrointestinal tract surgery.
10. Solid organ or stem cell transplantation.
11. *Candida* colonization.

The incidence of nosocomial IC has continued to rise over the past two decades in parallel with advances in medical and surgical

procedures. Basetti et al⁷, in a retrospective study of candidemia in Italy found that the incidence of candidemia increased from 1.25 in 1999 to 3.06/10 000 patient-days/year in 2003. Candidemia due to non-*albicans* species markedly increased and a logistic regression analysis showed a statistically significant correlation between the shift from *albicans* to non-*albicans* strains and the yearly fluconazole consumption. Similar findings were observed by Celebi et al⁸, wherein they reported that nosocomial candidemia significantly increased from 3.2 cases per 1000 admissions in 1997-99 to 5.5 per 1000 admissions in 2000-2002 and to 6.9 per 1000 admissions in 2003-2005. Presterl et al⁹ also found that the incidence rate of *Candida* spp. in blood cultures increased from 0.27 cases/1000 admissions in 2001 to 0.77 cases/1000 admissions in 2006 (p<0.005). Chakarbarti et al¹⁰ in a retrospective evaluation of candidemia in an Indian teaching hospital over a 10-year period observed that the incidence of patients with candidemia increased eleven-fold in the second half of the study period (55 patients) compared with the first half (5 patients). Haematological malignancies, neonatal septicaemia, cardiac abnormalities and cardiac surgery were the commonest underlying diseases in these patients. Intravascular catheter use for over 24 h (78%) and neutropenia (48%) were the accountable predisposing factors. Prolonged hospitalization (mean average 22.2 days as compared with 11.2 days in other patients) was an added risk factor in these patients.

DIAGNOSTIC DELEMNAS

Given that rapid initiation of appropriate antifungal therapy is crucial for reducing mortality, prompt diagnosis of infection is of the utmost importance. Unfortunately, diagnosing invasive fungal infections remains difficult and is often delayed. Invasive candidiasis can involve virtually any organ, and, as such, has a variety of clinical manifestations. With few exceptions, there are no distinctive and unique clinical features that are sufficiently predictive of IC to guide specific antifungal therapy. Fever is often the only clinical clue of invasive candidiasis on a high risk patient. So, persistent unexplained fever or sepsis that is not responding to broad spectrum antibiotics may be the setting for the more acute forms of invasive candidiasis. In about 15% of neutropenic patients with invasive candidiasis, a characteristic macronodular rash will appear. The rash may be isolated (extremities, abdomen) or may cover the entire body. Many candidaemic patients have one or more retinal lesions that may represent candida endophthalmitis, but then these are relatively non-specific and may appear similar to lesions caused by diabetes or hypertension. Radiological signs appear often late in the course of infection, which again result in delayed diagnosis.

The most basic form of invasive candidiasis is Candidemia, which

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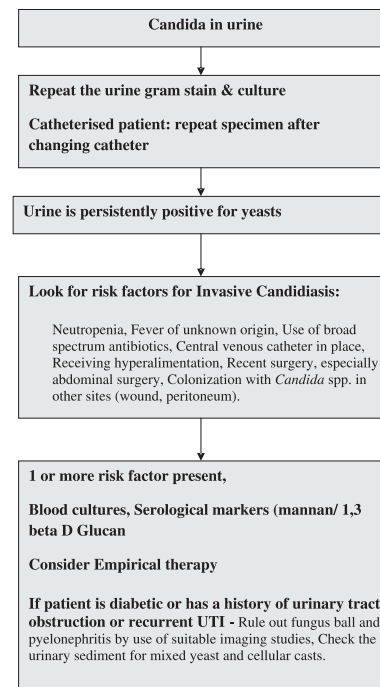
occurs in 50% to 70% of patients with this disorder. Unfortunately blood cultures are an insensitive and delayed means of diagnosing IC. As many as 50% of patients with autopsy-proven disease had negative blood cultures antemortem. Newer blood culture techniques probably have increased overall sensitivity to around 70%, but there remain significant numbers of patients who have IC in whom all routine blood cultures are negative. Histopathology may be useful for demonstrating tissue invasion, but then invasive tissue sampling is often problematic in critically ill patients and also species identification is not possible by histopathology. Because of the difficulty in establishing a firm diagnosis of IC clinically and the limited usefulness of blood cultures, nonculture diagnostic techniques have better predictive value. Serological tests consist of detection of components of the fungal cell wall, such as mannan, galactomannan and β -(1,3)-D-glucan, or antibodies directed against these antigens (antimannan) in blood or other body fluids. 1,3 β -glucan assay probably is the most reliable, with a sensitivity and specificity of 70% and 87%, respectively, among patients who have proven IC¹¹. Molecular diagnostic tests for detection of *Candida* DNA in either blood or tissues have generated interest but are not yet standardized or readily available in most clinical laboratory settings nor have they been validated in large clinical trials. Thus, no single test is available to make a straightforward diagnosis on invasive candidiasis. Instead, a physician must combine his or her knowledge of the patient's risk factors for invasive candidiasis, clinical signs that might suggest candidiasis, and a mosaic of investigations to make an early diagnosis. Diagnosis of infections due to *Candida* species presents unique problems. Although culturing *Candida* spp from a normally sterile body site other than urine is usually diagnostic of disease, culturing them from sputum, bronchoalveolar fluid, abdominal drains, epithelial, or mucocutaneous sources can cause confusion as these organisms commonly colonize human skin and mucous membranes so that merely isolating them in culture specimens from these sites is not proof of invasion.

CANDIDURIA: SIGNIFICANCE?

The presence of yeast in the urine, whether microscopically visualized or grown in culture, must be evaluated in the context of the particular clinical setting to determine its relevance and the need for antifungal therapy. The finding of *Candida* organisms in the urine may represent contamination, colonization or infection. Contamination of a urine specimen is common, especially if the specimen is a suboptimal urine collection from a catheterized patient or a woman who has heavy yeast colonization of the vulvovestibular area. "Colonization" usually refers to the asymptomatic adherence of yeast, usually on drainage catheters or other foreign bodies in the urinary tract (i.e., stents and nephrostomy tubes). This may spuriously result in a high concentration of the organisms on urine culture. There is no reliable method for differentiating colonization from infection. Unlike bacteriuria and bacterial urinary tract infections, neither microbiological quantification of *Candida* colonies or the concomitant presence of pyuria are good guides to identify disease and rule out colonization. A Systematic Approach to the Urine Culture Positive for *Candida* spp. is depicted in fig 1.

If there is no predisposing condition like catheterization, diabetes, etc. in an asymptomatic patient, only observation is warranted. Among patients with predisposing conditions, management of that condition alone, e.g. removal of an indwelling catheter, may be sufficient to eliminate candiduria without specific antifungal therapy. Treatment of asymptomatic candiduria is recommended in patients following renal transplantation, low-birth-weight infants, in the

Fig 1: A Systematic Approach to the Urine Culture Positive for *Candida* spp.



presence of or following neutropenia, and as a prophylactic measure in patients about to undergo invasive urologic procedures.

CANDIDA ISOLATION FROM OTHER SPECIMENS?

Because of the rarity of *Candida* pneumonia, the extremely common finding of *Candida* in respiratory secretions, and the lack of specificity of this finding, a decision to initiate antifungal therapy should not be made on the basis of respiratory tract culture results alone. Similarly, the clinical interpretation of *Candida* spp. isolated from an abdominal drainage site is difficult. However, there is evidence that an isolate obtained from an intraoperative specimen must be considered as producing an infection in many instances. Thus, it is imperative that the laboratory report isolations of *Candida* spp. from intraoperative samples even when multiple bacterial species are isolated from the same specimen.

COLONISATION V/S INFECTION

The significance of *Candida* colonization as a predictor of invasive disease has been an issue of debate over the last 2 decades, in fact, it is most appropriate to view *Candida* colonization at any clinically important site as a risk factor and not as a disease. Furthermore, differentiation between *Candida* colonization and invasive candidiasis (IC) is difficult. In fact, many patients in the ICU setting with *Candida* species colonization are not given antifungal agents, despite many of them having IC, whereas a large number of patients are treated with antifungals empirically without a definite diagnosis of IC, resulting in a substantial increase in the use of antifungal drugs, cost of treatment, and risk of emergence of resistant species. For any particular patient, it is difficult to predict the likelihood of contracting an invasive fungal infection using published clinical data because local factors and conditions greatly contribute to overall risk. This explains the wide variation in infection rates recorded by individual observers.

Growth of *Candida* in semiquantitative cultures from multiple body sites has been used, to predict the risk for invasive candidiasis. The “Colonization Index”, calculated by dividing the number of colonized sites by the number of cultured sites, was found to be significantly higher in patients who developed invasive candidiasis than in control individuals (0.70 ± 0.17 versus 0.47 ± 0.17 ; $P < 0.01$)¹². More recently, based on a prospective, cohort, observational, multicentre study that included 73 medical-surgical ICUs in Spain¹³, a ‘Candida score’ was developed with the aim being to initiate antifungal therapy early. An adjusted logistic regression model indicated that surgery on ICU admission, total parenteral nutrition, colonization at multiple sites with *Candida* and severe sepsis were associated with an increased risk for proven *Candida* infection. Patients with a *Candida* score, calculated using these variables, of 2.5 or more were 7.5 times more likely to have *Candida* infections than patients with a score of less than 2.5.

Most recently, an analysis of risk factors in 2,890 patients who stayed in the ICU for more than 4 days led to the development and validation of a clinical prediction rule for the early diagnosis of invasive candidiasis in the ICU¹⁴. The best prediction rule used a combination of the following factors: any systemic antibiotic or presence of central venous catheter and at least two other risk factors, including total parenteral nutrition, major surgery, pancreatitis, use of steroids and immunosuppressive agents. This prediction rule exhibited a sensitivity of only 34%, a specificity of 90%, a positive predictive value of 10% and a negative predictive value of 97%. This clinical rule may therefore help clinicians to rule out invasive candidiasis. However, data on the use of these risk assessment scores for guiding patient management are not yet available and their clinical utility remains to be established in prospective clinical studies.

THERAPEUTIC CHALLENGES:

Epidemiology changes

Until recently, *C. albicans* was by far the predominant species in most countries, causing up to two thirds of all cases of invasive candidiasis. However, a shift toward non-*albicans* *Candida* species has been observed¹⁵. In India also, increasing isolation of non-*albicans* from blood stream infections have been reported with rates ranging from 77 to 92.6% with preponderance of *C. tropicalis*^{16,17,18,19}.

Although more than 90% of invasive infections due to *Candida* spp. are attributed to five species—*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*—the list of reported species continues to grow as laboratories are pushed to provide an identification to the species level is an aid in optimizing therapy of candidal infections.

Given the increased numbers of immunocompromised individuals worldwide, an ever-increasing number of previously “nonpathogenic” species are truly emerging as opportunistic pathogens. There are several species that merit discussion because either they appear to be increasing in frequency and have been shown to cause clusters of infection in the hospital setting, or they exhibit decreased susceptibility to one or more antifungal agents and therefore pose a threat of emergence in certain settings. *C. guilliermondii* has been responsible for clusters of infection in the hospital setting, and demonstrate decreased susceptibility to fluconazole. *C. rugosa* is reported to exhibit decreased susceptibility to both polyenes and fluconazole and may cause catheter-related fungemia in seriously ill patients. *C. inconspicua* and *C. norvegensis* like *C. krusei* exhibit intrinsic resistance to fluconazole²⁰. More recently, *C. haemulonii*, a yeast species previously known to cause an epidemic disease afflicting laboratory animals and onychomycosis in humans, has emerged as

an opportunistic fungal pathogen that is capable of causing an outbreak of fungemia. Although rarely isolated in clinical microbiology laboratories, *C. haemulonii* has been reported to be resistant to amphotericin B and azoles, wherein the only treatment option may be echinocandins²¹.

C. glabrata has an associated mortality rate of 49%. The risk of mortality is significantly increased in patients with prior abdominal surgery (overall risk (OR) = 2.8, $P = 0.001$) and patients with elevated creatinine (OR = 2.2, $P = 0.05$), and significantly decreased following the administration of amphotericin B (OR = 0.2, $P < 0.001$)²². The emergence of *C. krusei* may also have a profound effect on future clinical outcomes. A comparative study of fungemia in immunocompromised patients revealed that the mortality rate associated with *C. krusei* is 49% compared to a rate of only 28% with *C. albicans*. Antifungal response rates are also lower with *C. krusei*, although amphotericin B achieves a success rate of 51%²³. There is growing evidence suggesting this epidemiological shift is due to increasing use of azoles. Also, several non-*albicans* spp. (e.g., *C. glabrata* and *C. krusei*) exhibit resistance to traditional triazole antifungals like fluconazole, with cross-resistance to newer triazoles, posing a therapeutic challenge.

Chakrabarti et al²⁴ reported that among *Candida* BSI isolates, although *C. tropicalis* was the most common yeast isolated, significantly higher isolation of *C. guilliermondii* (30.4%) and *C. pelliculosa* (17.6%) was noted in paediatric patients; and *C. albicans* (26.3%) and *C. glabrata* (10.5%) in adult patients. Rare species like *C. ustus* (0.7%) and *Trichosporon asahii* (2.1%) were also isolated. Emergence of resistance to azoles (fluconazole, itraconazole, voriconazole) in *C. albicans* (12.5-18.8%) and *C. tropicalis* (10.2-13.6%) was also noted. The changes in epidemiology and the emergence of antifungal resistance, have led to permanent changes in medical practice, wherein fluconazole may not be a suitable agent for empirical treatment. Hence, it is important to monitor resistance trends, and the distribution of *Candida* spp. in the face of increasing usage of potent, broad spectrum antifungal agents.

Antifungal therapy

Treatment of candidemia is often found to be inadequate due to a delay in initiation of therapy, use of inappropriate class of agents and inadequate dose or duration of treatment.

Antifungal susceptibility testing in vitro is playing an increasing role in antifungal drug selection, as an aid in drug development studies and as a means of tracking the development of antifungal resistance in epidemiologic studies. Despite the perception that amphotericin B and its analogs are broadly active against *Candida* species, evidence is accumulating that suggests less-than-optimal activity against a number of species. *C. glabrata* and *C. krusei* exhibit decreased susceptibility to amphotericin B compared with *C. albicans*. *C. lusitanae* is notorious for developing clinical resistance to amphotericin B. *C. haemulonii* and *C. pseudohaemulonii*, have shown increased MICs and frank resistance to both amphotericin B and fluconazole and even exhibited clinical failure²⁵.

The broad use of fluconazole has given rise to concerns regarding the emergence of resistance to this class of antifungal agents. Apart from *C. krusei* (intrinsic resistant) and *C. glabrata*, *C. guilliermondii*, *C. rugosa*, *C. inconspicua*, and *C. norvegensis* have also shown reduced susceptibility to fluconazole. Cross-resistance between fluconazole and the extended spectrum triazoles (voriconazole, posaconazole, and itraconazole) is well described among isolates of *C. glabrata*.

Echinocandins provide excellent clinical efficacy coupled with low toxicity for the treatment of serious candidal infections. However,

recent reports²⁶ describing the emergence of caspofungin resistance raise concerns about the emergence of caspofungin-resistant *Candida* spp. The knowledge of recent, local epidemiologic trends and susceptibility to antifungals is thus critical in this context.

Prevention and Prophylaxis

Given the increased morbidity and mortality due to IC and the difficulties in diagnosing and treating these infections, effective preventive strategies have a better chance of decreasing mortality than advances in therapy. Preventive measures to combat nosocomial candidemia including improved hand hygiene, optimal catheter placement and care, and prudent antimicrobial use to prevent morbidity and mortality due to nosocomial candidemia. Use of prophylactic antifungal use is debatable. Several recent studies^{27,28,29} indicated that high-risk critically ill patients may benefit from antifungal prophylaxis. However, an important issue remains how to identify those patients who are likely to benefit from prophylaxis without unnecessarily exposing patients who are at either low or no risk of developing IC, to antifungal agents. According to a Cochrane review on antifungal agents for the prevention of fungal infections in non-neutropenic critically ill patients³⁰, ninety four patients should be treated with fluconazole to prevent one *Candida* infection. Whether antifungal prophylaxis may have an impact on mortality remains a matter of debate. The guidelines of the Infectious Diseases Society of America on treatment of candidiasis³¹ discourage routine use of antifungal prophylaxis in the general ICU setting. However, it was suggested that targeted prophylaxis with fluconazole should be considered in solid-organ transplant recipients, neutropenic patients and in high-risk patients in adult ICUs units with a high incidence of invasive candidiasis with a cumulative incidence of $\geq 10\%$.

CONCLUSION

Invasive candidiasis is the most frequent invasive mycosis in critically ill patients. Changing epidemiology with increased non-*albicans* *Candida* spp., nonspecific risk factors, insidious clinical presentation, and late diagnosis with culture-based methods coupled with the fact that no class of antifungal agent is immune to the development of resistance, are major challenges in the management of invasive candidiasis. Targeting patients with a high-risk profile, development of new noninvasive diagnostic tools for early diagnosis and therapy, and optimization of management strategies (i.e., prophylaxis, preemptive therapy, or empirical therapy) alongwith availability of new antifungal agents may allow us to overcome the ever-increasing threat of *Candida* infections.

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