

Study of risk factors and prevalence of invasive candidiasis in a tertiary care hospital

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Abstract

Introduction: The frequency of invasive mycoses has increased dramatically during the past two decades owing to medical advances such as intensive cancer chemotherapy, broad-spectrum antimicrobial therapy, invasive medical devices, organ transplantation, human immunodeficiency virus (HIV) disease epidemic and an expanding aging population. There were few Indian studies regarding the incidence and risk factors for candidemia. Hence the aim of this work was to evaluate the changes in the prevalence of candidemia and invasive candidiasis in a tertiary care hospital and also to assess the risk factors and predictors of mortality.

Materials and Methods: Nonsystematic review of patients with candidemia/invasive candidiasis was done during the period 1999 to 2004. All in-patients who had shown signs and symptoms of nosocomial blood stream infection were screened for candidial infection. Among these, 29 patients had candidemia/invasive candidiasis. Demographic and clinical data of these patients were recorded on a standardized form, which included age, sex, site of isolation, infectious diagnosis, underlying conditions, predisposing factors, catheter status and clinical outcome. The data were collected during the years of 1999 to 2004, which is divided into two time periods (1999-2001 and 2002-2004). Data collected during these different time spans are compared with each other.

Results: A total of 255 patients were screened during the study period. Among these, 100 patients were screened during the period 1999-2001 and 155 patients were screened during the year 2002-2004. Out of these patients, 29 showed positive cultures in blood or other sterile site (ascitic fluid, bronchial aspirate and urine from suprapubic puncture). Out of these, 24 were males and five were females. The most common risk factor was use of intravenous canulae (62.1%), followed by prolonged use of antibiotics (34.5%) and HIV infection (24.1%). There were no statistically significant differences in the risk factors during the two different study periods. *Candida* was mainly isolated from blood (75.9%). Other sources included ascitic fluid (10.4%), bronchial aspirate (3.4%), sputum (3.4%) and urine (6.9%). Distributions of sources were comparable during the two study periods. *Candida albicans*, *Candida tropicalis* and *Candida parapsilosis* caused 89.7%, 3.4%, 6.9% of the candidemia episodes respectively. The overall mortality was 51.7%.

Conclusion: The present study emphasizes the importance of candidemia among hospitalized patients. Continued surveillance of candidemia will be important to track trends of this serious infection and to document changes in its epidemiological features. More active screening in high-risk groups should be done to avoid diagnostic delay. Risk factors like prolonged use of multiple antibiotics, central venous catheters, mechanical ventilation and prolonged hospital stay should be restricted whenever possible. Timely use of antiretroviral drugs and other measures to improve the immunity of HIV patients may help to decrease the incidence of candidemia in this patient population.

Key words: *C. albicans*, candidiasis, human immunodeficiency virus infection, risk factors

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Introduction

The frequency of invasive mycoses has increased dramatically during the past two decades owing to medical advances such as intensive cancer chemotherapy, broad-spectrum antimicrobial therapy, invasive medical devices, organ transplantation, human immunodeficiency virus (HIV) disease epidemic and an expanding aging population. Mortality due to fungal infection increased three to four fold between 1980 and 1997, with mycoses ranking as the seventh leading cause of death in 1997 compared with tenth in 1980. Much of the increase during this period was due to HIV associated cryptococcosis and pneumocystosis; the rates of occurrence of both have since declined dramatically with the advent of more effective antiretroviral therapy and antifungal prophylaxis. Among patients who are not infected with HIV, however, invasive candidiasis and aspergillosis remain significant causes of morbidity and mortality. Current data from the surveillance and control of pathogens of epidemiological importance (SCOPE) surveillance system confirms that *Candida* species have become the fourth leading cause of blood stream infections.^[1] Candidemia is associated with increased cost and attributable mortality of 38%.^[2] Although *Candida albicans* is the most frequent organism encountered, a number of reports have documented infections caused by *C. tropicalis*, *C. glabrata*, *C. parapsilosis* and *C. krusei*.^[3,4] Non-*albicans Candida* species and other filamentous fungi also have emerged as significant pathogens in recent years.^[5] Careful epidemiologic studies have identified intravascular catheters, broad-spectrum antibiotics therapy, mucosal colonization, neutropenia, previous surgical procedures (particularly complicated abdominal surgery), total parenteral nutrition and concomitant bacteremia as significant risk factors for invasive candidal infection.^[6-8]

There were few Indian studies regarding the incidence and risk factors for candidemia. Hence the aim of this work was to evaluate the changes in the prevalence of candidemia and invasive candidiasis in a tertiary care hospital and also to assess the risk factors and predictors of mortality.

Materials and Methods

Nonsystematic review of patients with candidemia/invasive candidiasis was done during the period 1999 to 2004. All in-patients who had shown signs and

symptoms of nosocomial blood stream infection were screened for candidial infection. Among these, 29 patients had candidemia/invasive candidiasis. Demographic and clinical data of these patients were recorded on a standardized form which included age, sex, site of isolation, infectious diagnosis, underlying conditions, predisposing factors, catheter status, steroid treatment, chemotherapy, culturing and clinical outcome. The criterion for inclusion in the study was age above 12 years with positive fungal culture in hospitalized patients. Children below the age of 12 years and patients with less than 48h of hospital stay were excluded. The major reason for their hospital admission was some other underlying condition other than candidemia. The data were collected during the years of 1999 to 2004. This period is divided into two different time spans i.e., 1999-2001, 2002-2004. Data collected during these different time spans are compared with each other. Strains of *Candida* isolated from blood or other normally sterile sites in hospital laboratories were sent to central laboratory for further analysis.

Blood culture was performed using the automated blood culture system (Bact/alert). Five ml of blood/sterile body fluid was inoculated into Myco F Lytic medium. Culture bottles were loaded into the instrument and remained there for seven days or until designated positive. Subsequent subculture was done for speciation. Patients who showed positive cultures analyzed for predisposing factors for candidemia. These factors were analyzed for their association with mortality.

Statistical analysis was performed using Chi square test, fisher's exact test and student 't' tests

Results

A total of 255 patients were screened during the study period. Among these, 100 patients were screened during the period 1999-2001 and 155 patients were screened during the year 2002-2004. Out of these patients, 29 showed positive cultures in blood or other sterile site (ascitic fluid, bronchial aspirate and urine from suprapubic puncture). Out of these, 24 were males and five were females.

Table 1 summarizes the distribution of underlying diseases. Table 2 shows the risk factors within this population of patients with candidemia. At the onset of

Table 1: Distribution of underlying diseases

| Underlying diseases | Year | | Total (n=29) (%) |
|------------------------------------|------------------|----------------------|------------------|
| | 1999-2002 (n=14) | 2003-2004 (n=15) (%) | |
| Human immunodeficiency virus | 4 (28.6) | 3 (20) | 7 (24.1) |
| Neutropenia | 1 (7.1) | 0 | 1 (3.5) |
| Chronic obstructive airway disease | 0 | 1 (6.7) | 1 (3.5) |
| Pancreatitis | 1 (7.1) | 0 | 1 (3.5) |
| Infective endocarditis | 1 (21.4) | 0 | 3 (10.4) |
| Tuberculosis | 2 (14.3) | 1 (6.7) | 3 (10.4) |
| Typhoid fever | 1 (7.1) | 1 (6.7) | 2 (6.9) |
| Malignancy | 1 (14.3) | 1 (6.7) | 3 (10.4) |
| Burns | 1 (7.1) | 0 | 1 (3.5) |
| Sepsis | 0 | 4 (26.7) | 4 (13.8) |
| Poisoning | 1 (14.3) | 1 (6.7) | 3 (10.4) |
| Diabetes mellitus | 0 | 2 (13.3) | 2 (6.9) |
| Fracture | 1 (7.1) | 1 (6.7) | 2 (6.9) |

Table 2: Distribution of risk factors for candidiasis

| Risk factors | Year | | Total (n=29) (%) |
|------------------------|------------------|----------------------|------------------|
| | 1999-2002 (n=14) | 2003-2004 (n=15) (%) | |
| Prolonged antibiotics | 8 (57.1) | 8 (53.3) | 10 (34.5) |
| IV canula | 8 (57.1) | 10 (66.7) | 18 (62.1) |
| Prolonged fever | 2 (14.3) | 0 | 2 (6.9) |
| Steroid use | 3 (21.4) | 1 (6.7) | 4 (13.8) |
| Pneumonia | 2 (14.3) | 2 (13.3) | 4 (13.8) |
| Tuberculous meningitis | 1 (7.1) | 1 (6.7) | 2 (6.9) |
| Surgery | 1 (7.1) | 3 (20) | 4 (13.8) |
| Ventillator | 3 (21.4) | 1 (6.7) | 4 (13.8) |
| Fracture | 1 (7.1) | 1 (6.7) | 2 (6.9) |
| Organ failure | 2 (14.3) | 2 (13.3) | 4 (13.8) |

candidemia, all patients had at least one predisposing factor. The most common risk factor was use of intravenous canulae (62.1%), followed by prolonged use of antibiotics (34.5%). But the careful scrutiny of cases showed that IV canulae might be the risk factor in only two patients who had typhoid fever. Other patients with IV canulae had various other risk factors. Most common underlying disease was HIV infection (24.1%). There were no statistically significant differences in the risk factors during the two different time periods. Most of the patients had multiple risk factors. Out of the 27 patients, nine had two different risk factors, six had three risk factors, seven had four risk factors, five had five risk factors, one had six and another one had seven risk factors.

Candida was mainly isolated from blood (75.9%). Other

sources included ascitic fluid (10.4%), bronchial aspirate (3.4%), sputum (3.4%) and urine (6.9%). Distributions of sources were comparable during the two time periods [Table 3].

Table 4 shows the distribution of *Candida* species among the culture positive patients. *Candida albicans*, *Candida tropicalis* and *Candida parapsilosis* caused 89.7%, 3.4%, 6.9% of the candidemia episodes respectively. Distributions of species were similar during the two time periods except that *Candida tropicalis* was isolated in one patient during the period 2002-2004.

The overall mortality was 51.7%. There was no statistically significant difference in the outcome during the two time periods [Table 5]. Risk factors in patients

Table 3: Source for fungal isolation

| Source | Year | | Total (n=29) (%) |
|--------------------|----------------------|----------------------|------------------|
| | 1999-2002 (n=14) (%) | 2003-2004 (n=15) (%) | |
| Ascitic fluid | 0 | 3 (20) | 3 (10.4) |
| Blood | 13 (92.9) | 9 (60) | 22 (75.9) |
| Bronchial aspirate | 0 | 1 (6.7) | 1 (3.4) |
| Sputum | 1 (7.1) | 0 | 1 (3.4) |
| Urine | 0 | 2 (13.3) | 2 (6.9) |

Table 4: Species of *Candida*

| Species | Year | | |
|------------------------|----------------------|----------------------|------------------|
| | 1999-2002 (n=14) (%) | 1999-2002 (n=15) (%) | Total (n=29) (%) |
| <i>C. albicans</i> | 13 (92.9) | 13 (86.7) | 26 (89.7) |
| <i>C. parapsilosis</i> | 1 (7.1) | 1 (6.7) | 2 (6.9) |
| <i>C. tropicalis</i> | 0 | 1 (6.7) | 1 (3.4) |

Table 5: Outcome of candidiasis

| Outcome | Year | | |
|-----------|---------------|---------------|------------------|
| | 1999-2002 (%) | 2003-2004 (%) | Total (n=29) (%) |
| Died | 7 (50) | 8 (53.3) | 15 (51.7) |
| Responded | 7 (50) | 7 (46.7) | 14 (48.3) |

Fisher's exact test ($P=0.576$)

who died during the two time periods were comparable. Mortality was seen mainly in patients with HIV as the underlying disease and in those who had multiple risk factors. There was no statistically significant difference in age distribution of patients during the two time periods. Comparison of age versus outcome (mortality) also did not show any statistical significance.

Discussion

The present study emphasizes the importance of candidemia among hospitalized patients. Candidemia is not only associated with a significant mortality but also extends the duration of hospital stay and increases the cost of medical care. Patients with candidemia usually present with acute septic syndrome that is indistinguishable from bacteremia, but they may also exhibit a more indolent course manifested by fever of unknown origin. Major risk factors for candidemia include intravascular catheters, broad-spectrum antibiotics and immunosuppression.

The present study highlights the importance of candidemia among patients infected with HIV, in addition to the high risk groups such as, patients with IV canula, parenteral antibiotics, malignancy, surgery etc. The predisposing factors and underlying diseases observed in this study are comparable to those observed by others.^[6-9] Though the study data suggest IV canulae as the major risk factor, careful scrutiny of cases showed that IV canulae may be the important risk factor in only two patients with typhoid fever. In all other cases patients had other risk factors also. Abdominal surgery was one of the important risk factor, which indicates that source of candida is endogenous and probably the gut which have been colonized.

Our study confirms the importance of surgery, cancer, HIV infection and hematologic malignancies as factors contributing to nosocomial candidemia. Our patient population included 7 HIV patients (24.1%). In the United States the proportion of candidemia cases with HIV infection to all candidemia cases varied from 10% to 15%.^[10,11] The contribution of HIV infection as a predisposing risk factor for candidemia is further emphasized by a report from Italy, where *Candida* spp. was the third most common cause of nosocomial blood stream infections in HIV patients.^[12] In France, among cases of nosocomial candidemia, 13% of patients were reported to have HIV infection during 1990-1995 in one institution.^[13]

Central venous catheter as a risk factor for candidemia, has been discussed in many studies.^[8,14] A strong consensus has been emerged recently on the fact that intravenous lines should be withdrawn from candidemic patients whenever possible.^[15] More recently, a prospective multicenter study from a tertiary care hospital in Brazil demonstrated that non-removal of the central venous catheter, in addition to the older age, were the only factors associated with an increased risk of death.^[16]

Use of multiple antibiotics will suppress the bowel flora.^[17,18] Restoration of normal gut flora is the fundamental prerequisite for the control of fungal infections. This requires the restricted use of broad-spectrum antibiotics, which are known to affect the gut ecology.

Our result shows that *C. albicans* remains the *Candida* species most frequently implicated in nosocomial candidiasis with an overall frequency of 89.7%. We did

not identify any shift towards non-*C. albicans* species, in contrast to several reports from the United States, Australia and Europe.^[10,19-21] The male dominance which was observed in the present study is similar to that found in previous reports.^[10,22-24] Differences in candidemia rates between countries may also be attributable to differences in the study population, the prevalence of HIV infection in the study population and variations in patterns of healthcare delivery and clinical practices, including the frequency of using blood cultures in diagnosis. The differences may also be explained by differences in antibiotic use patterns and resistance situation.

The overall mortality was 51.7%. Despite antifungal treatment, the mortality of candidemia was high which indeed may reflect the severity of the already existing underlying diseases at the onset of candidemia, as well as direct mortality due to candidemia itself. The attributable mortality could not be assessed in the present study, as the study design did not include the matched control group. Study by Leleu *et al.* showed an attributable mortality as 31% in candidemia.^[25] This study was done by matching the patients with systemic candidemia to those without the evidence of systemic candidemia, but with similar underlying disease. Similarly, in another study, Gudlaugsson *et al.*, showed attributable mortality as 38% in nosocomial candidemia.^[26] Hence systemic candidemia is associated with high crude and attributable mortality which is much higher than that expected from underlying disease alone. Optimizing management of this infection is therefore imperative. Risk of death increases, if the treatment is delayed. Hence the empirical antifungal therapy, early in the course of suspected systemic candidiasis may improve the survival.

To a greater extent than for other fungi, treatment of candidemia can now be guided by *in-vitro* susceptibility testing. However, susceptibility testing of fungi is not considered a routine testing procedure in many laboratories and is not promptly available or is not universally considered as the standard of care. Knowledge of the infecting species, however, is highly predictive of likely susceptibilities and can be used as a guide to therapy. Susceptibility testing is especially helpful in deep infections due to nonalbicans species where the possibility of microbiological resistance must be considered.^[27]

Amphotericin B based preparations, azole antifungals and the echinocandin antifungal agents play a role in the treatment. Choice of therapy is guided by weighing the greater activity of amphotericin B based preparations and echinocandin antifungal agents for some non albicans species against the ready availability of oral and parenteral formulations for azole antifungal agents.^[27-28] Flucytosine has activity against many isolates of candida but is infrequently used. Use of amphotericin may be complicated by dose limiting nephrotoxicity and reducing the dose may compromise with clinical efficacy. Liposomal preparations of amphotericin are less nephrotoxic, but highly expensive. Flucanazole has excellent safety profile, but *Candida* species other than *C. albicans*, *C. glabrata* may become resistant to flucanazole during the course of treatment. In addition, there has been a major shift in the past decade towards nonalbicans species, which now account for half of cases of candidemia. Identification of candida species is thus important in this regard. The recent development of echinocandin has resulted in a new therapeutic alternative to amphotericin B and flucanazole for the primary treatment of candidemia and other forms of deeply invasive candidemia.^[29]

Prophylactic strategies are useful if the risk of a target disease is sharply elevated in a readily identified patient group. The role of fluconazole prophylaxis is well-established in neutropenic patients; however, among patients without neutropenia, such as surgical ICU patients, this role is less definitive.^[30] The emergence of non- *C. albicans* species as agents of candidemia has been attributed to the increasing use of azole drugs and resulting selection of species less susceptible to these agents. Role of azole chemoprophylaxis in development of drug resistance in *C. albicans* and in emergence of less susceptible fungal pathogens needs to be examined. Clinical practices in prophylaxis policies may vary a great deal between institutions and countries. While the prophylaxis effectively reduces the incidence of infections caused by fluconazole-sensitive species, the drug has an impact on the distribution of causative *Candida* species.^[30]

Present study included retrospective analysis of medical records from an individual hospital, which may not be representative of all hospitals serving a community. Analysis of population based laboratory surveillance may provide better understanding of epidemiological features

of candidemia, its incidence and species distribution. This may also help to avoid bias that results from including only selected referral institutions.

The prevention of nosocomial infections is an important aspect of patient care, particularly in high-risk areas such as intensive care units. Local hospital leadership needs to develop easily defined infection control policies that are evidence-based. These infection-control policies also require the presence of a dedicated group of infection-control practitioners to provide education, collect surveillance data and oversee the implementation of the local infection-control plan.

Treatment of underlying diseases, removal of possible risk factors and appropriate treatment with antifungals are all important steps in the management of systemic fungal infections. Although a number of risk factors for candidemia have been identified, consensus on preventive measures has not been achieved to date. Suggested methods for managements of central or peripheral IV catheters are still controversial. Strategies such as decreasing the number of antibiotics prescribed and azole chemoprophylaxis for high-risk group have been suggested, but not been widely implemented. Though the panel of experts reviewed the management and prevention of candidemia and developed consensus in this regard, data available to formulate these recommendations were limited and controversial. The effectiveness of prevention measures for candidemia, as well as cost- effectiveness and potential complications of such measures, require further evaluation. Continued surveillance of candidemia will be important to track trends of this serious infection and to document changes in its epidemiological features. More active screening in high risk groups should be done to avoid diagnostic delay. Risk factors like prolonged use of multiple antibiotics, central venous catheters, mechanical ventilation and prolonged hospital stay should be restricted whenever possible. Timely use of antiretroviral drugs and other measures to improve the immunity of HIV patients may help to decrease the incidence of candidemia in this patient population. Continued surveillance of candidemia will be important to document changes in epidemiological features of candidemia and antifungal susceptibilities.

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