ORIGINAL ARTICLE

An observational study of the risk factors and incidence of invasive fungal infections in ICU patients

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ABSTRACT

Background: The fungal infections have become a persistent health problem, still always remain under reported. A change in species distribution has been observed now a days with the emergence of many non-albicans candida species.

Objective: Our study aimed at evaluating the incidence of invasive Candidiasis (*Candida albicans* and non-*albicans*) and to assess the risk factors and predictors of mortality in seriously ill patients.

Methodology: This prospective, observational study was conducted at Division of Intensive Care Unit, Institute of Medical Science, BHU, Varanasi (India), during the period of 2009 to 2011. Patients with >8 out of 16 risk factors, e.g. prolonged antibiotic use, IV cannulation, steroid use etc, Candida scores (CS) > 2, Age >12 years and ICU stay >2 days were included in the study. Those with Candida scores > 3 were prophylactically given fluconazole.

A case report performa was completed for each patient, including demographic characteristics, dates of hospital and ICU admission and of discharge, vital sign status at discharge, previous treatment with antibiotics or immunosuppressive agents, presence of risk factors. Patients were followed till discharge from the ICU or death.

Results: Candida was isolated from blood in 53/206 patients. The P-value calculated in five risk groups, e.g. diabetics, patients receiving TPN, neutropenic patients, HIV and malignancy was significant ($P<0.05$). For all other risk factors P-value was >0.05. Over half of the Candida isolates recovered from blood were non-albicans species. The overall mortality in candidaemia patients was 37/53 (69.81%). Mortality was low with *Candida tropicalis* (57.7%) but number of patient was high among candida species.

Conclusion: Multiple risk factors were found to be associated with invasive fungal infection in critically ill patients. In the ICU population studied, candidemia was due to non-*albicans* spp. The importance of Candida scores on predicting mortality was also observed.

Keywords: Risk factors; Critically ill patients; Candida; Candidemia; Outcome

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INTRODUCTION

The fungal infections have become a persistent health problem. Invasive fungal infections, especially candidemia, have become the fourth most common cause (8%) of nosocomial blood stream infections (BSI).[1,2] Recent advances in medical science like broad spectrum antibiotics, total parenteral nutrition, invasive monitoring devices, organ transplantation and an ever-expanding aging population have resulted in a big rise in invasive fungal infections. Human immune deficiency virus (HIV) has a major role in this context. Mortality rate is high with invasive fungal infections.

Although *Candida albicans* is the most common organism isolated, a change in species distribution has been observed now a days with the emergence of many non-albicans Candida species. *C. glabrata* has emerged next to *C. albicans* in almost every survey in US hospitals,[3-6] whereas in other countries including India, *C. parapsilosis* and *C. tropicalis* are the main contenders.[1,5] Careful epidemiologic studies have identified factors like intravascular catheters, mucosal colonization, neutropenia, previous surgical procedures, total parenteral nutrition, broad-spectrum antibiotics therapy and concomitant bacteraemia or sepsis as significant risk factors for invasive fungal infections.

The aim of our study was to evaluate the changes in the prevalence of invasive Candidiasis, to assess the risk factors and predictors of mortality in patients admitted to Intensive Care Unit (ICU) of an academic tertiary care hospital, which caters for patients from the five states, namely Uttar Pradesh, Bihar, Madhya Pradesh, Jharkhand and Chhattisgarh. Our ICU is a sixteen bedded multispecialty unit.

METHODOLOGY

After getting due permission from the ethical committee, this prospective, observational study was conducted in Division of Intensive Care of Department of Anesthesiology. All patients admitted to ICU were screened for presence of risk factors for fungal infections, e.g. prolonged antibiotic use, IV cannulation, urinary catheterization, steroid use, intubation and ventilatory support, organ failure, hematological malignancy, diabetes mellitus (DM), neutropenia, severe/recurrent pneumonia, tracheostomy, total parenteral nutrition, hemodialysis, HIV infection and central lines insertion etc. Patients having >8 out of 16 risk factors were included in the study. These patients were further classified according to Candida score (CS) (i.e. 1 for TPN, 1 for surgery, 1 for multifocal fungal colonization and 2 for clinically severe sepsis). Those with CS of > 2 were included in the study. Patients aged >12 years and with ICU stay >2 days were included in the study.

Any of the following samples were obtained from the patients under strict aseptic precautions; blood at least from two sites (10 ml), endotracheal tube secretions collected in mucus extractor, bronchial aspirate, urine (50 ml), ascitic fluid (10 ml), central line tip (after removal), cerebrospinal fluid (2 ml), pericardial fluid (10 ml) and high vaginal swab, and were sent for culture/sensitivity.

Candidemia was defined as at least one positive blood culture for *Candida spp*. in patients with signs or symptoms of infection. Candiduria was taken when there was presence of more than 100,000 cfu/ml of the same *Candida spp*. in two distinct urine samples obtained within one week.

Identification of the fungus was done by fungal staining by KOH mount, then positive samples were cultivated in basal media like Sabarouds dextrose agar, and selective enriched media like the Brain-Heart infusion agar (BHIA). Thereafter the species identification was performed by performing fermentation reaction in glucose, sucrose, maltose and lactose and assimilation reaction (Table-1). Patients showing positive culture report or CS >3 were treated with fluconazole.

The recorded data were analyzed using chi-square test and Fisher's exact test. Data of this test were analyzed in SPSS version 16. Categorical variables were expressed as proportions (percentages), and numerical data as means (±standard deviations), medians, and ranges. Statistical significance was set at a *P* value of <0·05.

RESULTS

A total of 322 patients were selected, out of which 257 patients consented for a complete workup. The remaining 65 patients were excluded from the study. Four patients were left against medical advice within 4 days of admission so they were excluded. 47 patients expired within five days and we could not get their culture reports. These patients too, were excluded from the study. Finally 206 patients were enrolled in this study. Out of these, 53 patients were positive for Candida in their blood; of these, 31 were males and 22 females.

Table 1 compares distribution of risk factors among candidemia patients. Since IV cannula's and urinary catheters were put in all patients, these two risk factors were considered as constant and statistically insignificant. P-value was calculated using chi-square test and Fisher's exact test for risk factors including DM, malignancy, total parenteral nutrition, HIV, and neutropenia and was 0.045, 0.050, 0.048, 0.018 and 0.040 respectively, which are statistically significant (i.e. p<0.05). The p-value for all other factors like broad spectrum antibiotics (p = 0.24), central venous cannulation (p = 0.33), tracheostomy (p = 0.45), steroid therapy (p = 0.09), mechanical ventilation (p

Table 1: Distribution of risk factors among Candidaemia patients

Risk factor	No of patients n (%)		p value
	All (n=206)	Culture positive* (n=53)	
Broad spectrum antibiotics	196(95.1)	52(98.1)	0.240
Central venous catheter	157(76.2)	43(81.1)	0.330
Tracheostomy	69(33.5)	20(37.7)	0.450
Steroid	132(64.1)	39(73.6)	0.090
Ventilator	185(89.8)	50(94.3)	0.200
Diabetes	62(30.1)	10(18.9)	**0.045**
Malignancy	18(8.7)	8(15.1)	**0.050**
Organ failure	153(59.7)	28(52.8)	0.230
Neutropenia	41(19.9)	18(34.0)	**0.004**
Endotracheal tube	183(88.8)	48(90.6)	0.640
Pneumonia	81(39.3)	20(37.7)	0.780
Total parentral nutrition	89(43.2)	29(54.7)	**0.048**
Hemodialysis	36(17.5)	9(17.0)	0.910
HIV	2(1.0)	2(3.8)	**0.018**

*Cases with positive fungal culture in blood samples.

= 0.20), organ failure (p = 0.23), endotracheal intubation (p = 0.64), pneumonia (p= 0.78) and hemodialysis (p = 0.91) were statistically insignificant (p> 0.05).

Total cases of candida isolated from different sites were 53 out of 206; 53/206 (25.7%) being from blood. Other sites were urine (28.6%), central line tip (25.7%), endotracheal aspirate (25.2%), high vaginal swab (22.3%), pus (13.6%), bronchial aspirate (5.8%), ascitic fluid (4.9%) and pericardial fluid (0.49%).

Table 2 shows the distribution of Candida species (n=53) among blood culture positive patients. Over half of the Candida isolates recovered from blood were non-albicans species.

Table 2: Distribution of Candida species among blood culture positive patients. Data shown as n (%).

Candida species	No. of positive cases* (n = 53)
Candida tropicalis	26 (49.05%)
Candida albicans	14 (26.41%)
Candida gullerimondi	7 (13.20%)
Candida glabrata	4 (7.54%)
Candida krusei	2 (3.77%)

*Cases with positive fungal culture in blood samples.

Table 3 compares Candida score on day 1 and 7 with outcome. Of 181 patients with Candida score of 2 on day 1, 63.0% (114) expired and out of 25 patients with Candida score of 3, 48% patients expired. On day 7, 4 patients had CS of 2; out of these 2 (50%) patients expired. 159 had CS of 3; of these 95 (60.2%) patients expired. Out of the patients with CS of 4, 27 (65.9%) expired. The patients with Candida score of 3 or more on day 7 had had 61% mortality i.e. 122 out of 200.

Table 3: Comparison of Candida score on day1 and 7 with outcome. Data shown as n (%)

Candida score	Discharged	Expired	Total
Day 1			
2	67(37.0)	114(63.0)	181(100.0)
3	13(52)	12(48)	25(100.0)
Total	**80(38.8)**	**126(61.2)**	**206(100.0)**
Day 7			
2	2(50.0)	2(50.0)	4(100.0)
3	64(39.8)	95(60.2)	159(100.0)
4	14(34.1)	27(65.9)	41(100.0)
Total	**80(38.8)**	**124(61.2)**	**204(100.0)**

Table 4 compares the outcome in different Candida species. Mortality was 78.6%, 75.0%, 85.7%, 100% and 57.7% in *C. albicans*, *C. glabrata*, *C. gullerimondi, C. krusei* and *C. tropicalis* respectively.

Table 4: Comparison of outcome and Candida species recovered from blood.

Blood Culture	Outcome		Total
	Discharged	Expired	
Candida albicans	3	11	14
Candida glabrata	1	3	4
Candida gullerimondi	1	6	7
Candida krusei	0	2	2
Candida tropicalis	11	15	26
Sterile	64	89	153
Total	**80**	**126 (61.16%)**	**206**

Incidence of *C. tropicalis* topped the list among patients receiving TPN and neutropenic patients. Surprisingly incidence of *C. gullerimondi* was high in cancer patients, and *C. albican*s was high in diabetic patients.

DISCUSSION

This study highlights the significance of invasive fungal infections in patients admitted to ICU. Fungal infections are one of the reasons for increased cost of medical care in ICU as investigations and therapeutic agents both are costly. Moreover, fungal infections are associated with high mortality. Resistance to antifungal agents shows a rising trend, because of irrational use of antifungal agents. Often, fungal infections run an indolent course making diagnosis very complicated and difficult.

The studies done in this prospect previously have most frequently involved either patients with hematologic or solid organ malignancies or surgical or immunocompromised patients, for example those with organ transplant or HIV exclusively.[7] Strength of this study lies in inclusion of patients from different specialties, including medical, surgical, cardiac, cardiothoracic, and neurosurgical and the trauma patients, which helps make our results more generalized to critically ill patients with mixed population comprising of all age groups above 12 years of age. The lower limit of 12 years was fixed as children below this age are usually admitted in pediatric ICU which is looked after by pediatricians.

According to previous studies the major risk factors for fungemia and Candida sepsis are the combination of severe underlying disease states, multiple surgical interventions and intravascular invasive lines and catheters, the use of broad spectrum antibiotics, TPN, injury and malnutrition associated immunosuppression, and intra-abdominal or intra-thoracic infection.[7-9] Along with these risk factors the present study also includes IV cannulation,

tracheostomy, urinary catheterization, pneumonia, endotracheal tube intubation, DM, organ failure and HIV. This study highlights the importance of candidemia among diabetic patients, in addition to other patients on high risk. The p value calculated in these five risk groups was significant. Central venous catheter and use of broad spectrum antibiotics as risk factors for fungal infection has been discussed in many previous studies.[10,11] But in our study, both these factors appeared insignificant. In recent years, TPN has been recognized as a risk factor for serious Candida infections. The series by Curry et al[11] noted that 67% of patients with fungemia had received TPN prior to infection. One factor responsible may be the need for prolonged IV catheterization. In vitro studies have shown that Candida readily grows in hyper alimentation solutions containing amino acids or lipid emulsions.[12,13] In this study, 55% of patients with Candida infections received TPN prior to infection. This is comparable to the study by Tsai CC et al.[14]

Although we have included corticosteroid therapy as a potential risk factor, it was not found to be statistically significant in contrast to other studies.[7,15,16] The steroid dose for replacement therapy like septic shock and for other reasons like COPD was not recorded, which could have been more useful and might have been significant in multivariate analysis.

Overall, non-albicans species incidence was higher compared to *C. albicans* as observed in most of the studies including Chakrabarti A et al (1996).[17] *Candida albicans* was isolated from 26.41% and non albicans Candida species from 73.59% of patients. The emergence of such a high rate of non-albicans Candida species indicates inadequate hospital care practices, as a majority of these species are exogenous in origin. Aggressive use of intravascular devices and poor hand washing techniques are probable reasons for nosocomial transmission via direct contact.[17] *C. glabrata* is more prevalent in the hospitals of the United States especially in adult wards. In India *Candida tropicalis* ranks first among non-albicans Candida species isolated from adult wards,[18-21] except during some outbreaks due to specific species.[22] In the present study the isolation of *C. tropicalis* from 49.5% of patients confirms this observation. *C. gullerimondii* is a relatively uncommon species of Candida that appears to be increasing in frequency as a cause of invasive candidiasis especially in Latin America.[23] In the present study it accounts for 13.2%.

CS was used to select the patients in our study and may be a reason for high incidence of Candida in our study (53 out of 206). Unexpectedly CS did not correlate with the outcome. Since p-value was not significant but as CS on day 7 increased to ≥3, mortality increased up to 66%. On day1, patients with CS of 2 had mortality of 63%, but patients with score of 3 had a mortality of 48%. Thus empirical antifungal therapy started on day 1 for those who had a score of 3 decreased mortality rate.

The overall mortality in our study population was 61.2%. A study by Leleu et al. showed attributable mortality as 31% in candidemia.[23] Similarly, in another study by Gudlauqsson et al., attributable mortality was 38% in nosocomial candidaemia.[24] Zautis et al[25] found that 30-day mortality rate was 44% in pediatric ICU at Children's Hospital of Philadelphia during the period from 1997 through 2004. Candidemia caused by non-*albicans* species is associated with higher mortality and more likely to occur in patients with medical devices or receiving steroids.[26] As in our study, the mortality is more in patients who were infected with *C. krusei* (100.0%), *C. gullerimondii* (85.7%), *C. albicans* (78.6%) and *C. glabrata* (75.0%) and least with *C. tropicalis* (57.7%). The reason may be use of fluconazole as empirical treatment in our study. *C. tropicalis* is more sensitive to fluconazole, so mortality is less in this group as compared to *C. krusei*, *C. gullerimondii* and *C. glabrata*, which are resistant to Azoles.

Limitations: In terms of limitations of our study, the small number of the candidemia patients (53/206) is an important limitation. The small number of patients with each of the candida spp. does not allow meaningful analysis of possible associations between the survival and mortality within individual Candida spp. The information about the prescription of antibiotics was inadequate.

CONCLUSION

Multiple risk factors were found to be associated with invasive fungal infection in critically sick patients. In the ICU population studied, candidemia due to non-*albicans* spp. was associated with higher mortality compared with candidemia due to *C. albicans*. More than half of the Candida isolates recovered from blood were non-albicans and C. gullerimondi. C. krusei showed higher mortality. The Candida scores seems to be important in predicting mortality as a score of 3 or more on day 7 was associated with a high mortality of 61%.

Conflict of Interest: None

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