Candida glabrata candidemia: An emerging threat in critically ill patients

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Abstract

Background: Candidemia is an important nosocomial blood stream infection in critically ill patients. Although several studies have addressed candidemia, very few have reviewed the impact of *Candida glabrata* candidemia in Intensive Care Unit (ICU) patients. **Materials and Methods:** The medical records of ICU patients between 2006 and 2010 were reviewed retrospectively. The epidemiology, clinical features and mortality related risk factors among our adult ICU patients were seen. **Results:** Among 144 episodes of candidemia, *C. glabrata* (*n* = 26; 18.05%) was the third most common species isolated. The incidence of *C. glabrata* candidemia was 0.21/1000 ICU admissions. The most common risk factors were prior exposure to broad spectrum antibiotics (100%), central venous catheter (100%), mechanical ventilation (76.9%), diabetes mellitus (50%), age >65 years (46.15%). Urine (23%) was the most common source of *C. glabrata* candidemia. Overall in hospital 30 days mortality rate due to *C. glabrata* fungemia was 53.8%. Patients who were treated with fluconazole showed better outcome than patients treated with amphotericin B. Renal failure requiring hemodialysis was the significantly associated with mortality in our study. **Conclusion:** *Candida glabrata* was the 3rd most common *Candida* causing candidemia in our ICUs with a incidence of 0.21/1000 ICU admissions. The outcome of ICU acquired *C. glabrata* candidemia was poor with 30 days mortality rate of 53.8%. Renal failure requiring hemodialysis was the only risk factor associated with mortality. Further studies are required to identify the other risk factors associated with mortality in *C. glabrata* candidemia.

Keywords: Candida glabrata candidemia, mortality, risk factors

Introduction

Candidemia is the fourth most common cause of hospital acquired infection. It remains an important cause of morbidity and mortality in critically ill patients in Intensive Care Units (ICU).[1] Despite the availability of effective antifungal therapy, mortality due to candidemia remains high ranging from 30% to 60%.[2-5] Recent epidemiological data also reveal a mycological shift from *Candida albicans* to the non-*albicans Candida* (NAC) species such as *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis* and *Candida krusei*.[1,6,7] It is considered that frequent use of fluconazole as antifungal prophylaxis has played a major role in the emergence of NAC species. Some of these species have been correlated with increased virulence and sometimes with increased mortality. *C. glabrata* candidemia is considered to be associated with higher mortality than other NAC.[8] Although several studies have addressed epidemiological and clinical characteristics of candidemia in ICU, very few have reviewed the mortality related risk factors for *C. glabrata* candidemia. We therefore reviewed the epidemiology, clinical features and the association of mortality with various risk factors among the ICU patients with *C. glabrata* candidemia.

Materials and Methods

All adult (>18 years of age) patients, admitted in medical and surgical ICU, with *C. glabrata* candidemia.

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During the study period of 2006–2010 were included. Clinical information on each episode was collected on a standardized data form. The medical records of patients were reviewed retrospectively and data including demographic characteristics, clinical features, risk factors (such as presence of central line, prior exposure to fluconazole, antibacterials and anticancer therapy, receipt of total parenteral nutrition (TPN), renal failure requiring hemodialysis, mechanical ventilation, malignancy), source of candidemia, antifungal therapy, and clinical outcome at 30 days were collected for analysis. Episodes of candidemia developing >48 h after ICU admission or 48 h or less following discharge were included in the study. Neonatal or pediatric fungemia cases were not included in the study. A patient was considered to have candidemia if *C. glabrata* was isolated from at least one blood culture. Source of candidemia was defined as a culture positive site with the same species. Risk factors over 30 days prior to the onset of candidemia were assessed.

Blood samples were processed using the automated system BacT/Alert (Biomerieux). Identification of the *Candida* was done on Mini API (Biomerieux) till 2009 and on Vitek 2 compact (Biomerieux) thereafter. Statistical analysis was conducted using SPSS for windows version 13.0 (SPSS inc., Chicago, IL). Fisher exact test or Chi-square test was applied for comparison of categorical variables. $P < 0.05$ were considered as statistically significant.

Results

During our 5-year study period, there were 144 episodes of ICU acquired candidemia in 144 patients from our adult ICUs. *C. tropicalis* (33.3%) was the most common species followed by *C. albicans* (29.8%), *C. glabrata* (18.05%). *C. glabrata* (*n* = 26) was the 3rd most common species responsible for candidemia in our adult ICUs. Overall the incidence of candidemia was 1.17/1000 ICU admissions. The incidence of *C. glabrata* candidemia in ICU ranged from 0.31 to 0.11/1000 admissions (overall incidence – 0.21/1000 ICU admissions) with a peak in the year 2006 and 2010. Figure 1 shows that there is a fluctuating incidence trend of *C. glabrata* fungemia in our ICUs. The mean age was 60.7 ± 14.3 years and 65.3% were males. The median time from ICU admission to onset of *C. glabrata* candidemia was 8 ± 13.8 days. Out of total 26 patients, 17 patients were admitted in the medical ICUs and only 9 patients in the surgical ICUs. The most common risk factors were prior exposure to broad spectrum antibiotics (100%), central venous catheter (100%), mechanical ventilation (76.9%), diabetes mellitus (50%), age >65 years (46.15%). 30.7% patients had received prior corticosteroid therapy and
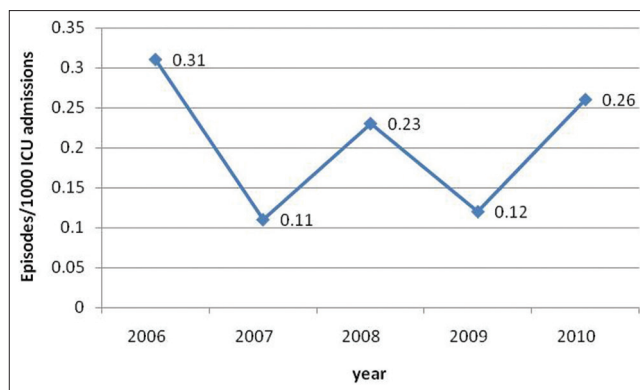

Figure 1: *Candida glabrata* incidence in Intensive Care Unit

26.9% patients had undergone hemodialysis for renal failure. 26.9% patients had a history of prior fluconazole exposure before blood culture came positive for *C. glabrata*. One patient each had a history of malignancy and autoimmune disease. Regarding the source of *C. glabrata* fungemia, urine (23%) was the most common source followed by endotracheal aspirates (19.2%). 50% patients did not have any source of candidemia. Of the 26 *C. glabrata* candidemia cases 15.3% (4/26), were not treated. This was due to death of the patients (*n* = 3) and discharge of the patient (*n* = 1), before blood culture positivity. Treatment regimens of *C. glabrata* candidemia patients is shown in Table 1. The most common antifungal agent given was the fluconazole (68.1%), followed by liposomal amphotericin B (13.6%). In 9.09% patients, antifungal therapy switched from fluconazole to amphotericin B either due to poor clinical response to fluconazole or identification of infecting species as *C. glabrata*. In our study, surprisingly 30 day's mortality rate was 42.9% in patients treated with fluconazole while 100% in patients treated with amphotericin B.

Overall in hospital 30 days mortality rate due to *C. glabrata* fungaemia was 53.8%, with a median time to death after drawing the first positive blood culture of 6 ± 7.7 days. The most common risk factor associated with mortality is shown in Table 2. Renal failure requiring hemodialysis was the only factor, which was significantly associated with mortality in our study.

Discussion

Candida glabrata currently ranks 2nd as the causative agent of nosocomial systemic *Candida* infections[8] and is associated with a high mortality rate.[1] According to a report by Pfaller and Diekema *C. glabrata* was an infrequent cause of blood stream infection in Latin America (7.5%) and Asia Pacific region (10.2%), while there is an increase in *C. glabrata* frequency in Canada, USA and Europe.[8] In our study, *C. glabrata* represents

Table 1: Treatment regimens of *Candida glabrata* candidemia patients

Antifungal therapy	Number (n=22) (%)
Fluconazole	15/22 (68.1)
Amphotericin B	3/22 (13.6)
Combination	2/22 (9.09)
Voriconazole	2/22 (9.09)

Table 2: Risk factors associated with mortality

Risk factor	Non survivors (n=14)	Survivors patients (n=12)	P
Age >65 years	7	5	0.671
ICU (medical: Surgical)	11:3	6:6	0.133
Use of broad spectrum antimicrobials	14	12	-
Use of corticosteroids	6	2	0.155
Prior fluconazole exposure	6	1	0.060
Central venous catheter	14	12	-
Receipt of total parenteral nutrition	3	0	0.140
Diabetes mellitus	7	6	1
Renal failure requiring hemodialysis	7	0	0.005
Mechanical ventilation	11	9	0.596
Anemia	2	2	0.641
Malignancy	1	0	0.538
Autoimmune disease	1	0	0.538

P<0.05: Significant. ICU: Intensive care unit

about 18.05% of candidemias which is consistent with rates reported in some studies (10–30%).[8-12] In a study done in Taiwan, candidemia incidence of 4.3/1000 ICU admissions was reported, which is quite higher than our incidence of 1.17/1000 ICU admissions.[13] Similar trend is seen in *C. glabrata* incidence (1.3/1000 ICU admissions in Taiwan when compared to 0.21/1000 ICU admissions in this study) in our study.[13] The incidence of *C. glabrata* candidemia was highest in the year 2006 (0.31/1000 ICU admissions) with a fluctuating trend in the studied time period in our ICUs. The reason for this could not be ascertained.

In a study done by Ruan *et al.*, 62% of the patients with *C. glabrata* candidemia was admitted in medical ICUs, which is similar to our data of 65.3%.[13] Many studies have reported an almost equal incidence among males and females; while in our study, 65.3% of *C. glabrata* candidemia was seen in male patients.[14,15]

Some of the previous studies have suggested that *C. glabrata* candidemia is more common in elderly patients.[16-19] This association can be due to antifungal drug pressure or underlying disease. Furthermore, Lockhart *et al.* demonstrated increased mucosal colonization with *C. glabrata* among healthy elderly individuals.[20] Our study also supports that *C. glabrata* candidemia is more common in elderly patients. The mean age in our study was 60.7 ± 14.3 years, which is comparable to other studies.[13,15]

As observed in some of the previous studies, increasing length of ICU stay increases the risk of candidemia.[14,21] Accordingly we report that median duration of ICU stay before *C. glabrata* candidemia was 8 ± 13.8 days. Choi *et al.* reports 15 ± 31 ICU days stay before *C. glabrata* candidemia, which is higher compared to our data.[14] Major risk factors for development of candidemia as reported in various other studies were also observed among our patients.[13-15,21] All the patients in our study were on broad spectrum antimicrobials and had central venous catheter. 76.5% patients were on mechanical ventilation, while in a study done by Ruan *et al.* 93% patients were mechanically ventilated.[13] In our study, only 26.9% patients were on hemodialysis due to renal failure which is quite lower than the rate reported (53%) by Ruan *et al.*[13] Ruan *et al.* reports that 53% of *C. glabrata* candidemia patients received TPN while in our ICU only 11.5% patients received TPN.[13] Although it should be kept in mind that the above factors are common to any patient admitted in ICU, and environment of ICU with various invasive procedures makes it conducive for acquiring fungal infections.

Our data suggests that candiduria is a useful indicator of systemic candidiasis and is more often seen with candidemia.[22] However, other studies report central venous catheter as a more common probable port of entry.[15]

The reported mortality rate for candidemia is very high (38–76%) in adults in developed as well as developing countries.[3,12,21,23-26] Several studies observed 30 days mortality rate for *C. glabrata* candidemia as 30%, 48.6%, 50%, 52%, 58%, 60%, which are comparable to our rate of 53.8%.[12-15,24,27,28] The median time from *C. glabrata* candidemia to death in our ICU was 6 ± 7.7 days. We also evaluated the modifiable risk factors associated with mortality. On univariate analysis, our data revealed that renal failure requiring hemodialysis was significantly associated with mortality (*P* = 0.005). Ruan *et al.*, Choi *et al.*, Blot *et al.* and Klevay *et al.* also reports renal failure as an independent predictor of mortality in *C. glabrata* candidemia.[14,15,27,28] They also report prior fluconazole exposure, age, use of steroids as predictors of mortality.

IDSA recommends Amphotericin B or caspofungin as the treatment for *C. glabrata* candidemia. *C. glabrata* is relatively resistant to fluconazole when compared with *C. albicans*. In our study, 68.1% of patients were treated with fluconazole. In a study done in Taiwan, amphotericin B regimen was associated with a lower mortality than regimens without amphotericin B.[13] While in contrast, our data shows that all three patients who were treated with amphotericin B died, while

only 50% of patients who received fluconazole died. This can be explained by the fact that in all the patients treated with amphotericin B, the treatment was started late (>72 h).

The present study had several limitations. First, the sample size was limited as the data is from a single institution and data could be influenced by local infection control practices and local antibiotic policies. Furthermore, *C. glabrata* candidemia is not very common infection. Second, the study was retrospective, which can lead to reviewer bias. Third, small sample size precludes meaningful statistical analysis of mortality related risk factors.

Conclusion

Candida glabrata was the 3rd most common *Candida* causing candidemia in our ICUs with an incidence of 0.21/1000 ICU admissions. The outcome of ICU acquired *C. glabrata* candidemia was poor with 30 days mortality rate of 53.8%. Renal failure requiring hemodialysis was the only risk factor associated with mortality. Further studies are required to identify the risk factors associated with mortality in *C. glabrata* candidemia.

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