Epidemiology of candidaemia in critically ill trauma patients: experiences of a level I trauma centre in North India

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There is a need to understand the epidemiology and risk factors associated with candidaemia in critically ill trauma patients. The rise in incidence of non-albicans candidaemia and the emergence of antifungal resistance have made such a study necessary. A prospective laboratory-based surveillance study was performed over a period of 21 months (April 2008–December 2009) at a level I trauma centre in New Delhi, India. All blood culture samples positive for Candida were processed for microbial identification by standard methods. Identification was carried out by conventional methods, using chromogenic medium (CHROMagar Candida) and by the automated Vitek 2 system. These isolates were characterized for their susceptibility to amphotericin B, fluconazole, flucytosine and voriconazole. Eighty-nine episodes of candidaemia occurred in 89 patients during the study period. The incidence was 0.71 episodes per 1000 patient days. A total of 136 Candida isolates were obtained, with non-albicans Candida species accounting for over 80%. Candida rugosa, a rarely isolated pathogen, accounted for 25 (18.4%) of the isolates, and 5.9% of the isolates were resistant to fluconazole. None of the isolates showed resistance against amphotericin B, flucytosine or voriconazole. The present study revealed that non-albicans Candida species caused most of the cases of candidaemia in the trauma patients. The isolation of C. rugosa from a large number of cases highlights the ability of this rarely reported pathogen to cause bloodstream infections. The presence of azole resistance among many of the Candida isolates is a matter of concern.

INTRODUCTION

Candida species are currently the fourth most common cause of bloodstream infections worldwide, and the third most common cause of bloodstream infections in the intensive care unit (ICU) (Beck-Sagué & Jarvis, 1993; Horn et al., 2009; Pfaller & Diekema, 2007; Wisplinghoff et al., 2004). Candidiasis is not only associated with a mortality of about 30–40%, but also extends the duration of hospital stay and increases the cost of medical care (Bodey et al., 1993; Lewis, 2009). Candidiasis is not only associated with a mortality of about 30–40%, but also extends the duration of hospital stay and increases the cost of medical care (Bodey et al., 1993; Lewis, 2009). Candida albicans has historically been the most frequent cause of candidiasis (Bodey et al., 1993). Although C. albicans remains the most commonly isolated species from cases of candidaemia in the USA, Europe and South America (Brazil), its dominance is slowly giving way to an increase in non-albicans species such as Candida glabrata (Colombo et al., 2006; Horn et al., 2009; Pfaller & Diekema, 2007; Tortorano et al., 2004). However, in Asian countries like India, Candida tropicalis appears to be emerging as the most common cause of candidaemia (Chakrabarti et al., 2009; Xess et al., 2007). Major risk factors for candidaemia include intravascular catheters, dialysis, burns, immunosuppression, use of steroids, diabetes, multiple abdominal surgeries, parenteral hyperalimentation and use of broad-spectrum antibiotics (Krcmery & Babela, 2002). The clinical presentations of patients with sepsis caused by C. albicans and non-albicans Candida species are indistinguishable. However, non-albicans Candida species are often less susceptible to fluconazole than C. albicans and may require a greater dosage of antifungals to cure clinically (Gómez et al., 2009).
Most reports of invasive candidiasis and *Candida* bloodstream infections are drawn from general hospital populations such as general surgery and oncology services (Dean & Burchard, 1996; Lewis, 2009). Few reports specifically concern the trauma patient population (Borzotta & Beardsley, 1999; Cornwell et al., 1995; Mahr et al., 1995). Trauma is the leading cause of death among persons below 44 years of age, and infection is second only to head injury as the leading cause of death. The nosocomial bloodstream infection rate in trauma patients, particularly in the ICU set-up, has been shown to be very high. Previous studies carried out in the USA have revealed infection rates ranging from 4 to 22% due to *Candida* species in trauma patients (Borzotta & Beardsley, 1999). There is a need to understand the epidemiology and risk factors associated with invasive candidiasis in previously less studied groups such as critically ill trauma patients. The rise in incidence of non-*albicans* candidaemia and the emergence of antifungal resistance have further fuelled the need to carry out such a study.

We performed a prospective study on the epidemiology of candidaemia at the JPNA Trauma Centre, All India Institute of Medical Sciences, New Delhi, India. We also evaluated the antifungal susceptibility profile of the *Candida* isolates thus obtained.

## METHODS

### Patient surveillance

A prospective laboratory-based surveillance study was performed over a period of 21 months (April 2008–December 2009) at the JPNA Trauma Centre, which is a 190-bed level I trauma centre in New Delhi, India. An episode of candidaemia was defined as the isolation of *Candida* species from a single positive blood culture. Candidaemia occurring in the same patient more than 30 days after an initial positive episode was considered to be a new episode (St-Germain et al., 2008). Demographic and clinical data were recorded using a standardized pro forma that contained the following information: age, gender, date of admission, ward/ICU, trauma type, date of candidaemia onset and underlying medical/surgical conditions such as hyperglycaemia, gastrointestinal tract perforation, exposure to invasive medical procedures such as central venous catheter (CVC) insertion, mechanical ventilation, blood transfusion, use of broad-spectrum antibiotics or corticosteroids, dialysis, management of candidaemia (e.g. antifungal treatment, catheter removal) and outcome.

### Blood culture and organism identification

For diagnosis of candidaemia/bacteraemia, 5–10 ml blood was collected in BacT/ALERT FA aerobic blood culture bottles (bioMérieux). The bottles were incubated and monitored regularly using the BacT/ALERT system (bioMérieux). All positive samples were processed for microbial identification by standard methods. Blood culture bottles positive for yeast cells were subcultured onto Sabouraud’s dextrose agar for further identification. Identification of these isolates was carried out by both conventional and automated methods. Conventional methods included a germ tube test, morphology on cornmeal agar (Hi-Media), reduction of triphenyltetrazolium chloride dye (Hi-Media), assimilation of various sugars and growth in the presence of cycloheximide. Growth on the chromogenic medium CHROMagar *Candida* (BD) and the automated Vitek 2 system ID-Yst cards were also used for identification.

### Antifungal susceptibility testing

Antifungal susceptibility to amphotericin B and fluconazole was tested using a broth microdilution method according to Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2008). Quality control was ensured by testing the CLSI recommended quality control strains *Candida parapsilosis* ATCC 22019 (fluconazole MIC range 1–4 µg ml⁻¹; reading at 48 h) and *Candida krusei* ATCC 6258 (fluconazole MIC range 16–128 µg ml⁻¹; reading at 48 h). Antifungal susceptibility to amphotericin B, fluconazole, fluconazole, and voriconazole was also performed with the Vitek 2 system using AST-Yst cards. The MIC breakpoints recommended by CLSI guidelines were followed (CLSI, 2008). For fluconazole and voriconazole, MIC breakpoints were as follows: sensitive, MIC ≤8 µg ml⁻¹ (fluconazole) and ≤1 µg ml⁻¹ (voriconazole); susceptible-dose dependent (SDD), MIC 16–32 µg ml⁻¹ (fluconazole) and 2 µg ml⁻¹ (voriconazole); resistant, MIC ≥64 µg ml⁻¹ (fluconazole) and ≥4 µg ml⁻¹ (voriconazole). For amphotericin B, isolates with MICs of ≥1 µg ml⁻¹ were categorized as resistant (CLSI, 2008). For fluconazole, each isolate was assigned to a susceptibility category according to the following MIC breakpoints recommended by the CLSI: susceptible ≤4 µg ml⁻¹, SDD 8–16 µg ml⁻¹ and resistant ≥32 µg ml⁻¹.

## RESULTS

### Patient population and clinical data

A total of 6519 blood culture samples were received in the microbiology laboratory of the JPNA Trauma Centre during the study period. The most commonly isolated organisms were coagulase-negative *Staphylococcus* (208 isolates, 3.2%) followed by *Staphylococcus aureus* (203 isolates, 3.1%), *Acinetobacter* species (202 isolates, 3.1%) and *Klebsiella* species (167, 2.6%). *Candida* was the fifth most commonly isolated group of organisms, with 136 isolates (2.1%) out of the total number of blood culture samples received. Eight of these were isolated (5.9%) concomitantly with bacteria (six with Gram-positive cocci and two with Gram-negative bacilli).

Eighty-nine episodes of candidaemia occurred in 89 patients out of a total of 3225 patients admitted to the trauma centre during the study period. The infection rate was 2.76% and the incidence was 0.71 episodes per 1000 patient days and 27.6 cases per 1000 admissions. The mean duration of hospital stay in the candidaemic patients was 39.1 days (range 8–109 days). Whilst seven patients did not have history of ICU admission throughout their hospital stay, the rest had an ICU stay of at least 1 week or more. These seven patients were admitted to the polytrauma ward of the hospital. Sixty-eight patients had episodes of candidaemia whilst they were in the ICU, whereas 21 episodes occurred in the wards of the trauma centre. Bloodstream *Candida* infections were diagnosed in 72 male patients and 17 female patients with ages ranging from 2 to 82 years (mean 35.4 years).

The most common injury that these patients suffered from was severe head injury, accounting for 65.2% (58/89), followed by severe injuries to the spine, chest and pelvis, contributing 13.5% (12/89), 3.4% (3/89) and 6.7% (6/89), respectively. The remaining 11.2% (10/89) of patients suffered from injuries resulting in gastrointestinal perfora-
tion. All of the patients (100%) were subjected to surgical interventions. The mean period after admission to the trauma centre after which Candida was isolated from the bloodstream was 20.4 days (range 4–96 days). The crude mortality rate in patients suffering from candidaemia was 50.6% (45/89). In contrast, the crude mortality rate for non-candidaemia patients admitted to the trauma centre over the same time period was 26.8% (841/3136). The difference between the two mortality rates was statistically significant (P<0.001). The percentage of candidaemic patients that were exposed to some of the major predisposing factors for candidaemia were as follows: broad-spectrum antibiotic therapy in 100% (89/89), multiple blood transfusions in 95.5% (85/89), mechanical ventilation in 94.4% (84/89), CVC insertion in 94.4% (84/89), hyperglycaemia in 24.7% (22/89) and steroid therapy in 18.0% (16/89).

Antifungal therapy in the form of systemic fluconazole was started in these patients within 24 h of detection of fungaemia. None had received prior antifungal therapy. Recent Infectious Diseases Society of America (IDSA) guidelines were followed for the management of candidaemia, i.e. administration of systemic antifungals for a period of 14 days after the last positive blood culture and resolution of signs and symptoms along with removal of intravenous catheter, wherever feasible. The blood cultures were repeated every week for surveillance and the duration of therapy was timed after the last positive culture.

In 10 out of 11 patients (whose isolates showed either dose-dependent susceptibility or resistance to fluconazole), antifungal therapy was modified on the basis of the antifungal susceptibility report. Antifungal therapy was switched to amphotericin B in these patients, with the exception of one patient who received caspofungin instead. One patient died before amphotericin B treatment could be initiated. The mortality in the patients whose therapy was modified was 50% (5/10).

Aetiology

As described above, a total of 136 Candida isolates were obtained, including 53 C. tropicalis (39.0%), 20 C. albicans (14.7%), 30 C. parapsilosis (22.1%) and eight C. glabrata (5.9%) isolates. Candida rugosa, an emerging fungal pathogen rarely isolated from clinical samples in India before, accounted for 25 (18.4%) of the isolates. Thus, non-albicans Candida species accounted for more than 80% of the isolates. The carbohydrate assimilation profile (determined using a modified auxanographic method) of the C. rugosa isolates revealed the following (+, assimilated; −, not assimilated): glucose +, maltose −, sucrose −, lactose −, galactose −, trehalose −, raffinose −, cellobiose −, melibiose +, inositol −, xylose +. This result matched the assimilation profile of C. rugosa. All isolates were identified as C. rugosa by the Vitek 2 system (99% probability, 'excellent' identification).

Considering the aetiology of candidaemia with respect to the number of patients/episodes, C. albicans was the cause in 15/89 patients (16.9%) in contrast to non-albicans Candida species in 74/89 patients (83.1%). Of the non-albicans species, C. tropicalis was responsible for causing the maximum number of episodes (29/89, 32.6%), followed by C. parapsilosis (21/89, 23.6%), C. rugosa (19/89, 21.4%) and C. glabrata (5/89, 5.6%).

CVC tips from seven patients (7.9%) and urine from 11 patients (12.4%) grew the same Candida species concomitantly with the blood isolates. The CVC tip isolates included C. tropicalis in three patients, C. rugosa in two patients and C. parapsilosis and C. albicans in one patient each. Similarly, the urine samples grew C. rugosa in six patients, C. tropicalis in four patients and C. albicans in one patient. Other samples that were concomitantly positive included one pleural fluid specimen (C. tropicalis), one bronchoalveolar lavage specimen (C. rugosa), one tracheal aspirate specimen (C. tropicalis) and one pus (wound discharge) specimen (C. tropicalis).

The crude mortality in patients suffering from non-albicans candidaemia was 54.1%, i.e. approximately 21% higher than in those suffering from candidaemia due to C. albicans. However, the difference was not statistically significant. On further analysis, a significant difference was noted between the crude mortality rates of cases of C. rugosa and C. parapsilosis candidaemia compared with those of C. albicans (68.4 vs 33.3%, P<0.05, and 61.9 vs 33.3%, P<0.05, respectively). However, it must be borne in mind that it is difficult to attribute the mortality of a patient with candidaemia to a specific cause, and the figures for mortality quoted above are not meant to prove an association between different Candida species and mortality. Univariate analysis of the risk factors associated with non-albicans candidaemia was carried out using a χ² test to evaluate categorical variables and a t-test to evaluate continuous variables (Table 1). CVC placement (P=0.008) was observed to be significantly associated with non-albicans candidaemia.

As C. rugosa had never been isolated from patients previously from our centre, a retrospective analysis to characterize the genetic relatedness among the C. rugosa isolates by random amplification of polymorphic DNA (RAPD) using the M13 primer was carried out (Behera et al., 2010). The RAPD patterns proved to be similar. However, we failed to isolate C. rugosa from other sites (such as beds, medical equipment used on patients, the hands of relatives and healthcare workers) and thus were not able to trace the possible source of this organism.

Antifungal susceptibility

Resistance was detected in 5.9% (8/136) of the isolates and a further 8.1% (11/136) were SDD for fluconazole. These strains were isolated from 12 patients (13.5%; 6/89 resistant and 6/89 SDD). The remaining isolates were sensitive to fluconazole. A large proportion of the C. tropicalis isolates (94.3%, 50/53) were sensitive to fluco-
azole. In contrast, the rates of susceptibility to fluconazole for *C. albicans*, *C. rugosa*, *C. parapsilosis* and *C. glabrata* isolates were lower: 85.0 % (17/20), 72.0 % (18/25), 83.3 % (25/30) and 87.5 % (7/8), respectively. Increased resistance to fluconazole (MIC $>64 \mu g/l$) was noted in *C. rugosa* (16.0 %, 4/25) and *C. glabrata* (12.5 %, 1/8). None of the isolates of *C. albicans*, only one of *C. tropicalis* (1.9 %) and two of *C. parapsilosis* (6.7 %) were resistant to fluconazole. These results are summarized in Table 2.

### Table 1. Univariate analysis of risk factors

Significant *P* values (*P*≤0.05) are indicated in bold. NA, Not applicable.

<table>
<thead>
<tr>
<th>Patients with candidaemia</th>
<th><em>C. albicans</em> (*n=15, 16.85 %)</th>
<th>Non-<em>C. albicans</em> (*n=74, 83.15 %)</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.07 ± 17.4</td>
<td>34.30 ± 17.02</td>
<td>0.67</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>46.72 ± 34.0</td>
<td>37.78 ± 25.46</td>
<td>0.35</td>
</tr>
<tr>
<td>Candidaemia onset (days)</td>
<td>21.55 ± 12.72</td>
<td>21.54 ± 19.85</td>
<td>1.00</td>
</tr>
<tr>
<td>Mechanical ventilation (days)</td>
<td>20.94 ± 19.76</td>
<td>24.77 ± 19.08</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Categorical variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (males)</td>
<td>10 (66.7 %)</td>
<td>67 (90.5 %)</td>
<td>0.01</td>
</tr>
<tr>
<td>Candiduria</td>
<td>1 (6.7 %)</td>
<td>10 (13.5 %)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>2 (13.3 %)</td>
<td>20 (27.0 %)</td>
<td>0.26</td>
</tr>
<tr>
<td>Steroids</td>
<td>1 (6.7 %)</td>
<td>15 (20.3 %)</td>
<td>0.21</td>
</tr>
<tr>
<td>Broad-spectrum antibiotics</td>
<td>15 (100.0 %)</td>
<td>74 (100 %)</td>
<td>NA</td>
</tr>
<tr>
<td>CVC</td>
<td>12 (80.0 %)</td>
<td>72 (97.3 %)</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>Dialysis</td>
<td>0 (0.0 %)</td>
<td>4 (5.4 %)</td>
<td>NA</td>
</tr>
<tr>
<td>Blood transfusion(s)</td>
<td>15 (100.0 %)</td>
<td>70 (94.6 %)</td>
<td>NA</td>
</tr>
<tr>
<td>ICU stay</td>
<td>12 (80.0 %)</td>
<td>70 (94.6 %)</td>
<td>0.056</td>
</tr>
<tr>
<td>Mortality</td>
<td>5 (33.3 %)</td>
<td>40 (54.05 %)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

None of the 136 *Candida* isolates were resistant to amphotericin B. Similarly, all the isolates were uniformly sensitive to flucytosine and voriconazole.

### DISCUSSION

This is the first description, to our knowledge, of *Candida* bloodstream infections in critically ill trauma patients in India. We have attempted to provide information on the epidemiology of candidaemia in this patient population and the antifungal susceptibility profile of the isolates obtained from them.

Incidence rates of candidaemia vary from region to region. Higher rates have been reported in developing countries such as Brazil (0.37 per 1000 patient days, 2.49 cases per 1000 admissions) (Colombo *et al.*, 2006) and Taiwan (2.88 per 1000 admissions) (Hsueh *et al.*, 2002) in comparison with developed countries such as the USA (0.46 per 1000 admissions) (Wisplinghoff *et al.*, 2004) and Spain (0.53 episodes per 1000 discharges or 0.73 episodes per 10000 patient days) (Almirante *et al.*, 2005), where the incidence is much lower. In our study, the incidence of candidaemia was 0.71 episodes per 1000 patient days or 27.6 cases per 1000 admissions. Critically injured patients have a high predisposition towards developing candidaemia, as typical risk factors (e.g. indwelling medical devices, prolonged ICU stay) occur commonly with them. This might explain the high incidence of candidaemia observed in our study. Only

### Table 2. Antifungal susceptibility profile to fluconazole of the 136 *Candida* isolates

All the isolates were susceptible to amphotericin B, flucytosine and voriconazole.

<table>
<thead>
<tr>
<th>Species (<em>n</em>)</th>
<th>Susceptible ($\leq 8 \mu g/ml$)</th>
<th>SDD ($16–32 \mu g/ml$)</th>
<th>Resistant ($\geq 64 \mu g/ml$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em> (20)</td>
<td>17 (85.0 %)</td>
<td>3 (15.0 %)</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td><em>C. tropicalis</em> (53)</td>
<td>50 (94.3 %)</td>
<td>2 (3.8 %)</td>
<td>1 (1.9 %)</td>
</tr>
<tr>
<td><em>C. parapsilosis</em> (30)</td>
<td>25 (83.3 %)</td>
<td>3 (10.0 %)</td>
<td>2 (6.7 %)</td>
</tr>
<tr>
<td><em>C. glabrata</em> (8)</td>
<td>7 (87.5 %)</td>
<td>0 (0.0 %)</td>
<td>1 (12.5 %)</td>
</tr>
<tr>
<td><em>C. rugosa</em> (25)</td>
<td>18 (72.0 %)</td>
<td>3 (12.0 %)</td>
<td>4 (16.0 %)</td>
</tr>
<tr>
<td>Total (136)</td>
<td>117 (86.0 %)</td>
<td>11 (8.1 %)</td>
<td>8 (5.9 %)</td>
</tr>
</tbody>
</table>
a few studies have studied the incidence of candidaemia in non-burn critically injured trauma patients. In their survey of 459 critically injured patients admitted at a level I trauma centre in the USA, Borzotta & Beardsley (1999) reported a candidaemia infection rate of 1.5% (15 per 1000 admissions). This figure, albeit lower than that observed in our study (2.76% or 27.6 per 1000 admissions), is still much higher than candidaemia rates in the general patient population. A striking finding of our study was a considerably significant difference in the mortality rates of candidaemia versus non-candidaemia patients (50.6 vs 26.8%, respectively; \(P<0.001\)). Patients with candidaemia are often very sick with multiple co-existing medical and surgical conditions and therefore it is difficult to attribute their cause of death as solely due to fungaemia. However, it is safe to speculate that the presence of candidaemia portends a poorer outcome in trauma patients.

An interesting observation of this study was that all patients were given broad-spectrum antibiotic therapy consisting of three or more drugs, a practice that can lead to suppression of commensal flora and increased proliferation of Candida species, especially in the gut. Similarly, all patients in our study underwent some form of surgical procedure, whilst an overwhelming majority had CVCs inserted. In addition, over 95% of the patients received multiple blood transfusions. Invasive procedures and blood transfusions have been speculated to have immunomodulatory and immunosuppressive effects, predisposing patients towards acquiring infections (Borzotta & Beardsley, 1999). Another interesting observation was that around ten patients in our study suffered from serious gastrointestinal injuries. Disruption of the integrity of the gastrointestinal barrier may cause commensal Candida species colonizing mucosal surfaces to invade the bloodstream. However, it is useful to bear in mind that the variables mentioned here cannot be taken as independent risk factors for the acquisition of candidaemia, as the analysis was univariate rather than multivariate.

In our study, non-albicans Candida species accounted for the majority of the episodes of candidaemia. Previous studies have shown high rates of carriage of this species on the hands of healthcare workers (Rangel-Frausto et al., 1999). Thus, the hands of healthcare workers could be one possible source of transmission. The use of intravascular devices may also have contributed to the acquisition of candidaemia. In our study, CVC placement was found to be significantly associated with non-albicans candidaemia (\(P<0.008\)). This may have been due to the fact that a larger proportion of patients with non-albicans candidaemia had a history of ICU stays compared with those with fungaemia due to C. albicans (70/74, 94.6%, vs 12/15, 80.0%, respectively; \(P=0.056\)). Whether this reflected an increased rate of carriage of non-albicans Candida species on the skin of these patients cannot be concluded by these findings. Nevertheless, the role of CVC placement and indwelling medical devices in promoting candidaemia has been reported in previous studies (Dimopoulos et al., 2008; Krcmery & Babela, 2002).

The trend of increasing rates of isolation of non-albicans Candida species from cases of candidaemia has also been observed at other tertiary care centres in India (Chakrabarti et al., 2009; Xess et al., 2007). Worldwide, the frequency of bloodstream infections due to C. tropicalis has increased (Pfaller & Diekema, 2007). In India, C. tropicalis ranks first among non-albicans Candida species in causing candidaemia (Chakrabarti et al., 2009; Xess et al., 2007). In the present study, C. tropicalis and C. parapsilosis were the two most commonly isolated species from cases of candidaemia. Thus, the species distribution in this study closely matched that of previous studies from North India. However, points in which this study differed from others were the lower isolation rate of C. glabrata (5.62%) and the absence of any case of candidaemia due to C. krusei. These findings probably reflect the absence of selective pressure exerted by azole antifungal prophylaxis at our centre, which would have led to isolation of species that are known to be inherently resistant to fluconazole such as C. krusei.

A unique aspect of our study was the isolation of a rare species, C. rugosa, from a large number of cases of fungaemia (19/89, 21.3%). Although isolated occasionally, C. rugosa has been cited as a distinct emerging cause of candidaemia. These infections are especially common among patients in ICUs. They are associated with typical risk factors such as indwelling central vascular catheters, broad-spectrum antibiotics and prior surgery (Mince et al., 2009).

Although C. rugosa infection is considered rare in humans, a large number of episodes of fungaemia due to C. rugosa were documented at a tertiary care teaching hospital in São Paulo, Brazil (Colombo et al., 2007). In addition, an outbreak of fungaemia due to C. rugosa in the same hospital was reported earlier (Colombo et al., 2003). In our experience, all C. rugosa candidaemic episodes have been documented in ICUs. Prior to this cluster, C. rugosa had never been identified as a cause of infection in our institution. Although the strains isolated in this study were genetically similar, the source of this possible outbreak could not be identified (Behera et al., 2010).

Results of antifungal susceptibility testing are important in guiding therapeutic decisions. In this study, 86% of the isolates were sensitive to fluconazole and 100% were sensitive to voriconazole. This is similar to the results of a recent update of the ARTEMIS DISK Global Antifungal Surveillance Study, which reported 90.2% susceptibility to fluconazole and 95.0% susceptibility to voriconazole in Candida isolates (Pfaller et al., 2010). This update also mentions that at least 30% of fluconazole-resistant isolates of C. albicans, C. glabrata, C. tropicalis and C. rugosa remained sensitive to voriconazole (Pfaller et al., 2010). This is noteworthy, especially as we observed no cross-resistance to voriconazole among the fluconazole-resistant isolates in our study. Our value for fluconazole resistance
(6.7 %, 6/89 patients) is close to the value of 7.1 % reported in the study by Chakrabarti et al. (2009). Furthermore we noted no resistance in C. albicans isolates and a low level of resistance among the C. tropicalis and C. parapsilosis isolates. In a previous study, we reported similar observations, with no resistance seen in strains of these commonly isolated species (Xess et al., 2007). In contrast, we observed a high level of resistance to fluconazole in C. rugosa strains, with 16.0 % (4/25) resistant and 12.0 % (3/25) SDD. The gradual emergence of resistance to azoles in C. rugosa has been noted before. In the previous updates of the ARTEMIS DISK Antifungal Surveillance Global Study, only 40.5 and 61.4 % of the C. rugosa isolates were susceptible to fluconazole and voriconazole, respectively (Pfaller et al., 2006a, b).

We observed no in vitro resistance to amphotericin B and flucytosine in any of the strains, which is in concordance with the findings of previously published data from India (Chakrabarti et al., 2009; Xess et al., 2007). However, the emergence of fluconazole resistance at our centre is a matter of concern and requires monitoring.

Azole antifungals were the most frequently administered antifungal agents in patients in our study, followed by amphotericin B. Prophylactic antifungal therapy was not given to any patient. The most recent invasive candidiasis treatment guidelines from the IDSA recommend fluconazole as the primary treatment for non-neutropenic patients with mild to moderate candidaemia and no recent azole exposure. An echinocandin antifungal is recommended as the primary therapy for non-neutropenic and neutropenic patients with moderately severe or severe candidaemia or those who have had recent azole exposure (Pappas et al., 2009). In spite of giving fluconazole as antifungal therapy in the majority of the patients in our study, the mortality remained high (~51 %). Echinocandins have been introduced recently for the treatment of candidaemia; however, their widespread use in Indian hospitals is still restricted by availability and high cost. This might explain why these agents were not used in this study for treatment of candidaemia, despite their proven efficacy. Other factors accounting for the high mortality seen in our study group could be the co-morbid medical conditions such as bacterial sepsis, ventilator-associated pneumonia, renal failure or acute respiratory distress syndrome that had developed in most of these patients.

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