Epidemiology of Candidemia in a Tertiary Care Centre of North India: 5-Year Study

I. Xess, N. Jain, F. Hasan, P. Mandal, U. Banerjee

Abstract

Background: To determine the distribution of species of *Candida* and the risk factors associated with candidemia in Indian population for which we conducted a retrospective study for 5 years in a tertiary care centre of North India.

Materials and Methods: Blood samples from 7,297 patients aged from 3 days to 85 years, suspected with candidemia, were collected and tested for *Candida*. The susceptibility patterns toward fluconazole for the year 2005 isolates were tested by micro-dilution assay as described in the CLSI (M27A-2 method).

Results: Most of the episodes have been caused by species other than *C. albicans*. Non-albicans candidemia was 79%–80% in both female and male populations. The most frequent species isolated from 275 patients in 5 years (January 2001–December 2005) was *C. tropicalis* (35.3%), followed by *C. albicans* (21.5%), *C. parapsilosis* (20%), *C. glabrata* (17.5%), *C. krusei* (3.3%), *C. haemulonii* (1.5%), and *C. guilliermondii* (1%). *C. parapsilosis* was the predominant in the fifth year of the study (2004–2005). Dose-dependant susceptibility to fluconazole was observed in 5% (n = 3) of the strains. Antifungal resistance was found in 11.7% (n = 7), which includes only *C. glabrata*.

Conclusion: These results were comparable to those derived from other regions of India. *C. tropicalis* has been reported as the predominant species involved in the cases of candidemia. But in 2005 it has moved toward *C. parapsilosis*. No true antifungal resistance is reported. Further epidemiological surveillance is needed.

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Introduction

Candida species are responsible for causing a number of invasive and non-invasive diseases. Blood stream infection is one of the life-threatening invasive disease causing significant mortality and morbidity. Clinical illness with at least one positive blood culture can confirm the candidemia. *Candida* sp. is the fourth most common pathogen associated with bloodstream infection worldwide [1, 2].

With the expanded use of antibiotic therapy and antifungals, the incidence of the candidemia has increased in recent years. The emergence of species resistance to antifungals has contributed to change the epidemiology of the disease. The mortality rate in cases of candidemia has been reported 38%–61% [3–7].

Initial reports suggest that *C. albicans* is the main etiological agent responsible for the cases of candidemia [7–9]. However non-albicans candidemia has increased in past few years [6, 10]. There are differences in prevalence of *Candida* sp. even in one hospital to another within the same region [11, 12]. The epidemiology of candidemia in India is not well studied till date, except a few studies in pediatric age group [13, 14].

Fluconazole and amphotericin B are the widely used drug worldwide. The side effects associated with amphotericin B limits its use. The azoles are much safer [15] but the resistance has been seen toward azoles in *Candida*. The resistant strains or the less susceptible strains for antifungal have been reported to be in circulation [16]. Therefore, antifungal susceptibility testing has become a need to predict clinical response, or at least to forecast failure. This is a retrospective study of *Candida*-related blood stream infection in AIIMS, New Delhi, India for distribution of species, their susceptibility pattern toward fluconazole and other risk factors associated with the disease.

Material and Methods

Patients and Blood Isolate

A retrospective study was done in 7,297 samples to determine the distribution of *Candida* species in blood stream infection in a tertiary care centre, New Delhi in between January 2001 and December 2005. Patient's consent has been taken for investigation by the institute during admission of the patient.

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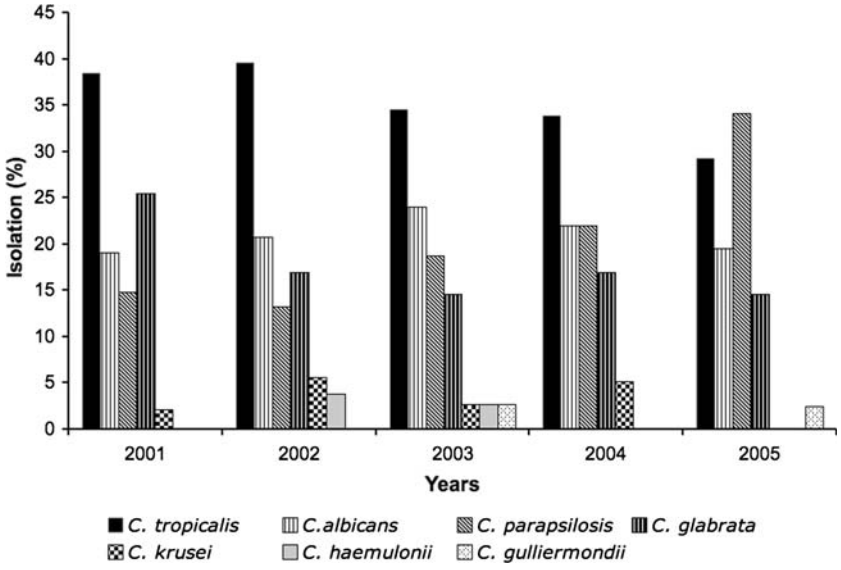

Figure 1. Distribution of *Candida* species (2001–2005) in blood. Note: Till 2004 *C. tropicalis* was the most frequently isolated species but in 2005 *C. parapsilosis* was isolated more frequently.

Five to ten mllilitres of blood was collected in a biphasic blood culture bottle and incubated at 37 °C for a maximum period of 1 month. The culture-positive yeast were speciated by conventional method.

In Vitro Antifungal Susceptibility Testing

The MICs toward fluconazole were determined in 2005 isolates by CLSI (formerly NCCLS) M27-A methodology. Micro dilution technique was carried out in 96-well micro-titer plates. As a quality control *C. parapsilosis* ATCC 22019 (fluconazole, 2 mg/l–8 mg/l) and *C. krusei* ATCC 6258 (fluconazole, 16 mg/l–64 mg/l) were included.

Results

Out of 7,297 samples, 439 samples (6%) were positive for *Candida* sp., which were isolated from 275 patients. The age of the patients ranges from 3 days to 85 years with infants (less than 1 year) making up 20.3% (n = 56). One hundred and four patients (37.8%) were females and 171 (62.2%) were males. Non-albican candidemia was 79%–80% in the populations.

The year-wise distribution of *Candida* species from (January 2001–December 2005) has been summarized in figure 1. We have also observed a high percentage of disseminated infection (15.6%) and one case of mixed infection of *C. tropicalis* and *C. glabrata* in an infant. Note that, fungi other than *Candida* were also isolated from 40 patients of fungemia [*Trichosporon* (n = 33), *Histoplasma* (1), *Cryptococcus neoformans* (n = 6)].

The distribution of *Candida* species among 275 patients according to age groups and patients with different underlying conditions has been summarized in figure 2. The most important predisposing factors in candidemia patients were; prior use of antibiotic in 196 patients (71.2%), ventilator and urinary catheter in 153 (55.6%), central venous catheter in 103 (37.5%), post-operative care in 115 (41.8%), and other miscellaneous factors including the gastric probe, parenteral nutrition and prematurity in 44 patients (16%). All the patients included in the study had more than one risk factor.

Antifungal susceptibility results: All Candida isolated in the year 2005 (n = 60) from 41 patients were tested for their susceptibility for fluconazole. The isolation includes *C. parapsilosis* (n = 22), *C. tropicalis* (n = 17), *C. albicans* (n = 11), *C. glabrata* (n = 9), *C. guilliermondii* (n = 1) and *C. Krusei* (n = 5). Dose-dependant susceptibility to fluconazole was observed in 5% (n = 3) of strains. It includes 1 *C. parapsilosis* and 2 *C. glabrata* isolates. Resistance was found in 11.7% (n = 7), which includes only *C. glabrata*. As the strain collection of 2005 has no *C. krusei*, we tested four isolates from previous year's collection. All the isolates were found to be resistant for fluconazole.

The mortality due to candidemia in year 2001–2004 was high; 168 out of 233 died, whereas in 2005 the mortality was much low, 20 out of 44 died of candidemia. The patients were treated with fluconazole or amphotericin B or voriconazole.

Discussion

Out of 87.3% of fungemia cases, *C. tropicalis* (n = 97, 35.3%) was predominant among *Candida* genus. Non-*albicans Candida* (78%, n = 215) is predominating over *albicans* which correlates well with studies associated with candidemina in India in recent years [10, 13, 14, 17–19]. Two studies from one hospital in India [19, 20] show a remarkable change in the distribution of species. In the first 10 years *C. albicans* accounted to 50%, but this decreased to 25% in the next 5 years, whereas there was a parallel increase in *C. tropicalis* from 15% to 36%. *C. tropicalis* was constantly the main species for 4 years (2001–2004). This may be because of the widespread use

of fluconazole, which would select the yeast species intrinsically resistant or less sensitive to fluconazole, such as *C. krusei, C. glabrata* or *C. tropicalis* [2].

Studies from Japan also show a low prevalence of *C. albicans* [21, 22], whereas, Brazil, Taiwan, Spain, Denmark and other countries worldwide revealed that *C. albicans* is the main agent associated with fungemia [23–25]. It confirms the variation of *Candida* species in different geographical regions.

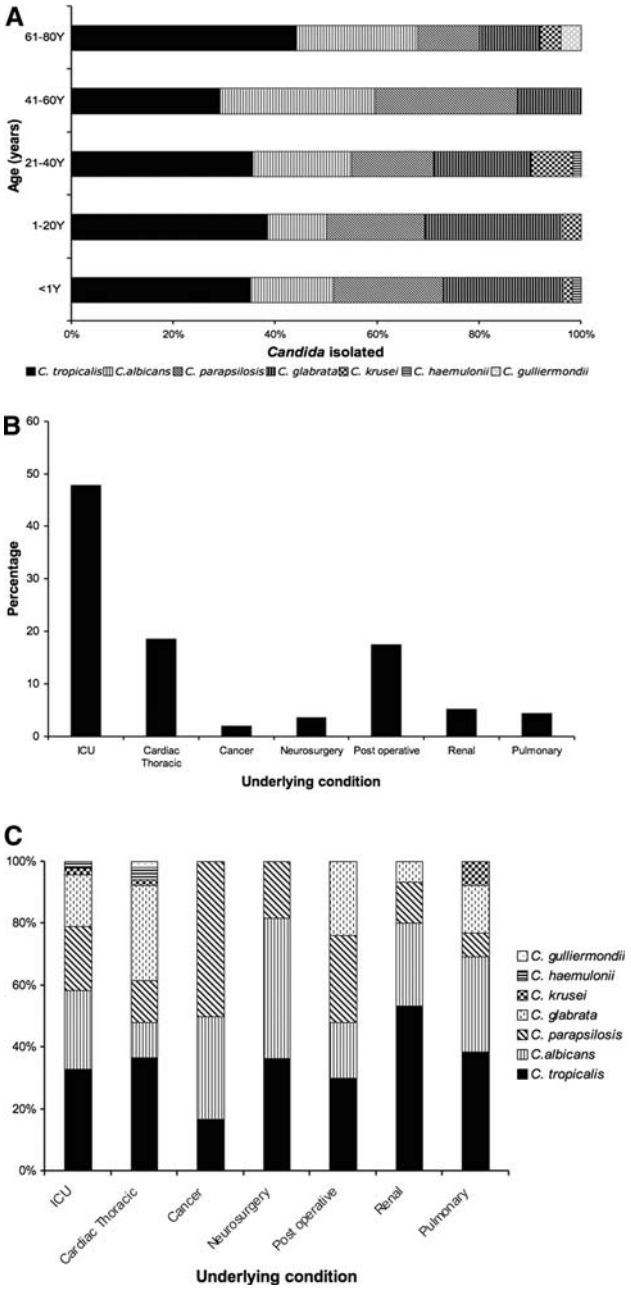

Figure 2. Underlying conditions and species distribution in candidemia. (A) Species distribution according age. (B) Different underlying conditions in candidemia patients. (C) Species distribution in each underlying condition.

Candida parapsilosis increased gradually between 2001 and 2005 from 15% to 34%. As a result, *C. parapsilosis* become the most predominant in 2005. Recently Brazil has also reported the frequent isolation of *C. parapsilosis* [6]. *C. parapsilosis* is known to cause fungemia among hospitalized patients and is known to form biofilm in glucosilated solution and adheres to plastic material such as catheter, gastric probes and parenteral nutrition tubes.

Antifungal treatment was started immediately after the first positive confirmation from blood after blood withdrawal for a second culture for repeat confirmation of candidemia. Standard antifungal therapy is the infusion of amphotericin B till culture comes negative then shifts on to fluconazole till the patient is symptomatic. If Voriconazole is the drug of choice, it is given for a week then there is a shift on to fluconazole.

Higher mortality was observed in *C. tropicalis* and *C. albicans* in comparison to other species. Though isolates of *C. parapsilosis* increased in 2005 yet the mortality rate was low. This finding can be explained by studies which have determined that *C. parapsilosis* is less virulent on animal models [26].

The resistance is still uncommon in *Candida* species recovered from blood culture [27]. The resistance is reported from 1.9% to 13% in *albicans* and non-*albicans* and the resistant strains of *C. tropicalis* were found highly similar by DNA fingerprinting [28, 29].

In our study, dose-dependant susceptibility to fluconazole was observed in 5% (n = 3) of strains. It includes one *C. parapsilosis* and *C. glabrata* strains. Antifungal resistance was found in 11.7% (n = 7), which includes only *C. glabrata*. Four isolates of *C. krusei* from previous year's collection were tested also and found resistant to fluconazole. In one study from India, resistance has been observed against fluconazole in *C. krusei*, *C. guilliermondii* and *C. tropicalis* [18], but we could not confirm the same in *C. tropicalis* isolates. The resistance was only documented in *C. glabrata* and *C. krusei*, which is intrinsically resistant to fluconazole. A shift in prevalence of *C. glabrata* from *C. albicans* has been reported. It can be probably linked to the use of fluconazole prophylaxis [30].

The mortality rate in the first 4 years was high; that is, 72.2% in our center, which is probably because of the unawareness of disease prevalence; but the following years showed the decreasing trends, that is 47% of mortality.

Candidemia prevalence rate is increasing worldwide in the last 10–20 years in all tertiary care hospitals worldwide. *C. parapsilosis* is emerging as the most common non-albican pathogen to cause candidemia. Resistance toward fluconazole of blood isolates is still low. Distribution of *Candida* species isolated from blood varies markedly between different geographical regions in the world.

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