Non-*albicans Candida* species in blood stream infections in a tertiary care hospital at New Delhi, India

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Background & objectives: During recent decades, there has been a change in the epidemiology of *Candida* infections, characterized by a progressive shift from a predominance of *Candida albicans* to non-*albicans Candida* species. This study was undertaken to analyze the change in the epidemiology of candidaemia and antifungal use at tertiary care hospital in New Delhi, India, over a period of 10 years.

Methods: A retrospective review of candidaemia between 1999 and 2008 and antifungal use from 2000 to 2008 was performed at Sir Ganga Ram Hosptial, New Delhi. Initially (1999-2005), isolates were differentiated as *C. albicans* and non- *albicans Candida* species. Between 2006-2008, these were identified to the species level and antifungal susceptibility was performed.

Results: The occurrence of candidaemia and total antifungal use increased significantly. Candidaemia due to non-*albicans* species increased and this was correlated with an increasing use of fluconazole. There was emergence and increased isolation of a novel species *C. haemulonii* with decreased susceptibility to both amphotericin B and azoles. Overall, sensitivities of 89.6, 90.9, 88.6, 68.8 and 54.3 per cent to amphotericin B, 5 flucytosine, voriconazole, fluconazole and itraconazole, respectively were observed. Cross-resistance or reduced susceptibility to both fluconazole (MIC >16 μg/ml) and voriconazole was observed in 11.3 per cent isolates.

Interpretation & conclusions: The study demonstrates a shift to non-*albicans Candida* species causing fungaemia and the emergence of amphotericin B and azole resistant novel species, *C. haemulonii*. Decreased susceptibility to fluconazole, as well as the threat of emergence of cross-resistance to voriconazole in the background of high azole consumption may limit the use of these agents as a presumptive therapy for *Candida* blood stream infections (BSI).

Key words Antifungal use - *Candida haemulonii* - candidaemia - fluconazole - non-*albicans Candida* species

Nosocomial candidiasis is gaining significance worldwide. Among the causes of bloodstream infection, *Candida* ranks fourth in the United States and seventh in Europe[1,2]. *Candida* blood stream infections (BSI) are associated with a very high crude mortality of over 60 per cent, while the attributable mortality may be as high as 49 per cent[3,4].

Until recently, *C. albicans* was by far the predominant species in most countries, causing up to two thirds of all cases of invasive candidiasis. However,

during recent decades, several countries around the world have witnessed a change in the epidemiology of *Candida* infections, characterized by a progressive shift from a predominance of *Candida albicans* to non-*albicans Candida* species (including *C. glabrata* and *C. krusei*)[5]. There is growing evidence suggesting a role for increasing use of azole agents in this epidemiological shift. Several of these non-*albicans Candida* species (*e.g.*, *C. glabrata* and *C. krusei*) exhibit resistance to traditional triazole antifungals like fluconazole, and may also demonstrate cross-resistance to newer triazoles[6]. This makes it imperative to perform both speciation and antifungal susceptibility testing of all yeast fungi isolated from bloodstream or otherwise.

Because of considerable regional variability, local epidemiological knowledge is critical in the effective management of invasive candidiasis. Only a few studies from India have reported candidaemia rates of 6-18 per cent[6,7] and an increase in isolation of non-*albicans Candida* species from blood samples[9,10]. But speciation and susceptibility testing of *Candida* is still not routinely being done at most of the centres. Further, no data are available from India regarding the estimation of antifungal use in hospitals. The aim of this study was to describe the change in the epidemiology of candidaemia and antifungal use at a tertiary care centre in New Delhi, India over a decade.

Material & Methods

This retrospective study was conducted at the Clinical Microbiology & Immunology Department of Sir Ganga Ram Hospital, New Delhi. Cases of candidaemia seen between 1999 and 2008 and antifungal use from 2000 to 2008 were included. Patient's consent had been taken for investigation by the hospital at the time of admission. All *Candida* species isolated from blood specimens submitted for culture from patients of all age groups and either sex clinically suspected to have septicaemia were included in the study. Positive blood cultures were considered as part of a single episode if they were of the same species and sensitivity and occurred less than two weeks apart.

Isolation and identification of yeast fungi: Clinical isolates of yeast obtained from blood culture using automated blood culture system BacT/ALERT 3D (bioMerieux, France) were included. Between 1999-2005, the isolates (n=583) were differentiated as *C. albicans* and non- *albicans Candida* species using classical methods, *i.e.* germ tube test (rabbit serum, BD, USA), colony morphology on cornmeal agar

(HiMedia, India). From 2006 onwards, the isolates (n=623) were identified to the species level using Vitek 2 YST identification card (bioMerieux, France).

Antifungal susceptibility testing: Antifungal susceptibility testing was initiated in 2006. Between 2006 and 2008, antifungal sensitivity was performed against amphotericin B (AMB), 5 flucytosine (5FC), fluconazole (FLU) and itraconazole (ITR) and voriconazole (VOR) by broth microdilution using API system [ATB FUNGUS 2 (173 isolates) and ATB FUNGUS 3 **(**259 isolates**)**, bioMerieux, France]. For isolates wherein API system was not recommended by the manufacturer, sensitivity was done using E test (40 isolates) (AB Biodisk, Sweden) against AMB, FLU and VOR. Results were interpreted as per the Clinical Laboratory Standards Institute (CLSI; formerly NCCLS) M27-A2 document[11]. Isolates with minimum inhibitory concentration (MIC) of <8 µg/ml for fluconazole, <0.12 µg/ml for itraconazole and <4 µg/ml for flucytosine were taken as sensitive. Isolates with MIC of <1 µg/ml for amphotericin B were considered susceptible as has been done by other authors[12]. Nguyen *et al*[12] in a study to demonstrate a correlation between results of *in vitro* susceptibility testing to amphotericin B using the standard method proposed by CLSI and microbiologic outcome for patients with *Candida* fungemia observed that a breakpoint MIC of >1.0 mg/ml had a 100 per cent specificity and a 100 per cent positive predictive value for identifying microbiologic failure. A resistant breakpoint for amphotericin B of >1 µg/ml for MLC (minimal lethal concentration) and >µg/ml for MIC could be inferred from the study. As per CLSI[14] a *Candida* isolate with an MIC of >1 µg/ml for amphotericin B is likely to be resistant. In case of voriconazole, MICs of <1 µg/ml were taken as sensitive[15].

C. parapsilosis ATCC 22019 and *C. krusei* ATCC 6258 were included as the control organisms for antifungal susceptibility test.

Antifungal use: The annual consumption of antifungal drugs from 2000- 2008 was determined from pharmacy data using Hospital Information System (Intersystems, USA), Speedminer (Malaysia). The antifungal drugs used for either prophylaxis or curative treatment of candidaemia were amphotericin B deoxycholate (AMBD), amphotericin B lipid complex (ABLC), liposomal amphotericin B (LAMB), fluconazole (FCZ) voriconazole (VCZ) and caspofungin (CAS). The consensus definition of prescribed daily doses (PDD

in adults defined according to locally used doses) was used[16]. These differ from the daily defined doses (DDD) as per WHO/ATC[17] definition which defines lower doses for amphotericin B and fluconazole (35mg & 200 mg, respectively). Antifungal drug use density was calculated as yearly PDD/100 patient-days or occupied bed days. The PDDs for the different drugs were: 70 mg for AMBD, 350 mg for ABLC, 210 mg for LAMB, 400 mg for FCZ, 400 mg for VCZ and 50 mg for CAS[18].

Statistical analysis: Trend analysis of incidence of candidaemia and antifungal use was done by using regression analysis of time trends for time series data. This analysis provided the rate of increase or decrease in the parameter/outcome of interest along with its standard error. The test of significance was applied for testing its relevance. Time trend analysis was done by fitting the time trend function $Y = ae^{bt}$. In this b was the percentage growth rate per year. The growth rate was tested for its significance using t-test. The results were presented providing the goodness of fit of time trend along with *P* value for its significance. Pearson correlation coefficients (r) were calculated to assess the relationship between fluconazole consumption and isolation of non-*albicans Candida* species over time (2000-2008) using SPSS software version 17 (Chicago IL software).

Results

Distribution of candidaemia cases: A total of 69,010 blood cultures were analyzed. Among these, (1206; 1.74%) were found positive for *Candida* species. The average number of cases with candidaemia was 6.84 episodes /10,000 patient-days/ year (range 2.46-11 episodes) Fig. 1 (inset). Overall rate of change of candidaemia from 1998 to 2008 was 17.7 per cent (r^2=0.743; *P*=0.001). From 1999-2008, the value increased from 1.61 to 2.75 and 1.03 to 8.29 episodes/ 10, 000 patient-days in the wards and ICU settings, respectively (Fig. 1). The rate of change in candidaemia in the ICU over the study period was 29.5 per cent which was significant (r^2=0.823; *P*<0.001).

Distribution of Candida spp.: The percentage of *C. albicans* which was isolated in about 76 per cent of the episodes in 1999, progressively dropped to 15.2 per cent in 2008, the absolute number and the incidence of *C. albicans*, however, did not significantly vary during the years observed (2.01-1.67 episodes/ 10,000 patient-days). On the other hand, isolation of non-
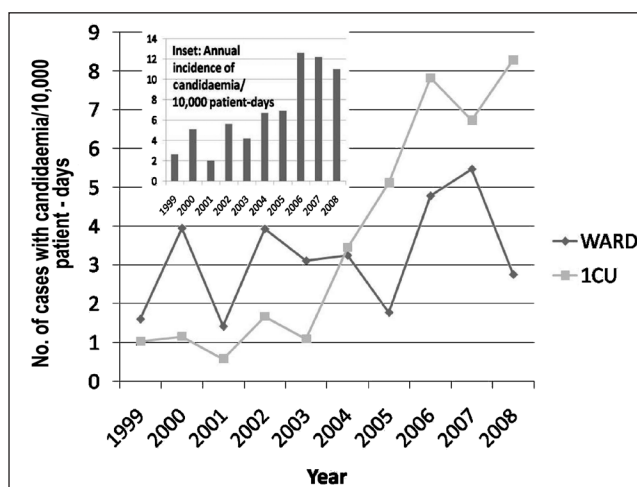

Fig. 1. Candidaemia cases in ward and ICU settings. Inset: Annual incidence of candidaemia.

Candida species increased from 0.633 in 1999 to 9.38 episodes/ 10,000 patient days in 2008 (Fig. 2) with the rate of change over time being 28.9 per cent, which was significant (r^2=0.834; *P*<0.001).

Between 2006 and 2008, *C. tropicalis* was the most common species (182 cases; 29.2%), followed by *C. albicans* (105 cases; 16.8%) and *C. haemulonii* (97 cases; 15.5%). *C. parapsilosis* and *C. glabrata* were isolated in 78 (12.5%) and 53 (8.5%) cases, respectively. These five species constituted 82.6 per cent of the isolates. *C. krusei* was isolated in only 11 cases, *C. pelliculosa* 23 cases, *Pichia ohmeri* 10 cases, *C. rugosa* 9 cases and *Trichosporon* spp. 7 cases. Twenty one cases were due to unusual isolates with <5 isolates each (*C. guilliermondi, C. utilis, C. famata, C. lusitaniae, Yerwonia* spp., *Stephanos ciferii* and *Saccchromyces cerevisiae*). Twenty seven *Candida*
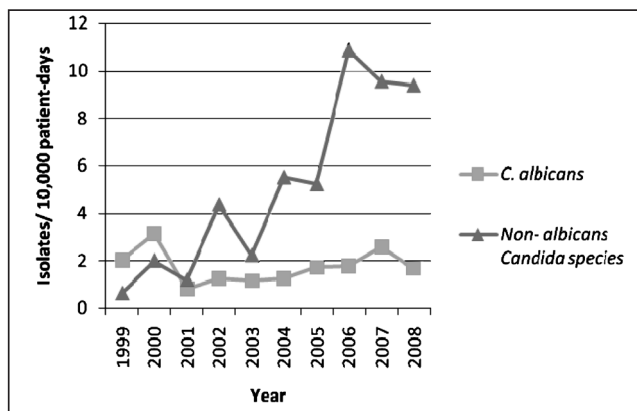

Fig. 2. Incidence of candidaemia due to *C. albicans* and non-*C. albicans Candida* species. No. of episodes/10000 patient - days.

isolates could not be speciated. *C. haemulonii* was first isolated in 2006 and its isolation increased from 5.45 per cent in 2006 to 18.2 per cent in 2008.

Antifungal drug use: The annual usage of antifungal drugs between 2000-2008 is illustrated in Fig. 3. Total antifungal use increased between 2000 and 2008 from 0.627 to 8.77 PDD/ 100 patient-days with the rate of change over time being 32 per cent which was statistically significant (r^2=0.99, *P*<0.001). Fluconazole was the most frequently prescribed antifungal drug and rate of change of increase in its usage over time between 2000-2008 was 25.1 per cent (r^2=0.971, *P*<0.001). There was also a significant increase in amphotericin B (conventional and lipid formulations) usage from 0.007 to 1.92 PDDs/ 100 patient days with a rate of change of 56.2 per cent over the study period (r^2=0.74, *p*=0.006). Voriconazole and caspofungin usage started in 2006 and 2008, respectively. Between 2006-2008, voriconazole usage almost doubled from 0.71 to 1.22 PDDs/ 100 patient days, though it was not statistically significant. There was a statistically significant correlation between yearly fluconazole use and increase in isolation of non- a*lbicans Candida* species (*P*=0.006).

Antifungal susceptibility: The sensitivity profiles of all *Candida* isolates are shown in the Table. Between 2006 to 2008, data on amphotericin B, 5 flucytosine, fluconazole and itraconazole susceptibility were available for 472, 432, 472 and 432 isolates, respectively. Voriconazole susceptibility testing was performed from 2007 thus results were available for 299 isolates. The susceptibility profile of all *Candida* isolates showed that 90.9 per cent were sensitive to 5

Fig. 3. Yearly antifungal use (2000-2008) in term of prescribed daily dose (PDD)/100 bed-days.

flucytosine, 88.6 per cent to voriconazole, 68.8 per cent to fluconazole and 54.3 per cent to itraconazole.

Nearly all the isolates (89.6%) had an MIC of <1 µg/ml for amphotericin B, the notable exception being *C. haemulonii* where only 27.6 per cent isolates demonstrated an MIC of <1 µg/ml. *C. haemulonii* was also completely resistant to both fluconazole and itraconazole whereas it showed 63.8 per cent sensitivity to voriconazole. In addition, 11 isolates were tested against caspofungin by E test and all were sensitive (MIC <2 µg/ml)[14].

C. tropicalis, the most common species isolated, was 90.5 per cent susceptible to fluconazole, whereas *C. parapsilosis* and *C. glabrata* showed lower sensitivity rates of 66.1 and 60.8 per cent, respectively. Of the 299 isolates for which, both fluconazole and voriconazole susceptibility data were available, 112 were resistant or showed reduced susceptibilities to fluconazole (MIC >16 µg/ml) and 34 of these were resistant or showed reduced susceptibilities to voriconazole (MIC >2 µg/ml). These included *C. haemulonii* (17 isolates), *C. tropicalis*, *C. glabrata* and *C. parapsilosis* (3 isolates each), *C. famata* (2 isolates) and unidentified *Candida* species (6 isolates).

Discussion

The current retrospective analysis of candidaemia over a 10-yr period revealed a five-fold increase in candidaemia cases at our centre. Data from the NNIS system on nosocomial BSIs has also shown up to five-fold increase in incidence between 1980 and 1989 in the United States[19]. However, Chakarbarti *et al*[20] in a retrospective evaluation of candidaemia in an Indian teaching hospital over a 10-year period have observed even higher rates of increase ranging from eleven-fold in the second half of 1980s and a further 18-fold in 1995 compared to 1991[21]. These studies suggested wide variations in the prevalence of candidaemia in different hospitals in India.

The observed increase in candidaemia cases in our study was probably due to the greater use of invasive devices, broad-spectrum antibacterial agents, more extensive surgical procedures and use of advance life support on various transplant patients. Between 2000 and 2008, there was an increase in the number of blood cultures (4380 to 8608) alongwith total number of surgeries (17768 to 23874) and organ transplants (71 to 294) performed representing an increase in number of cases at a higher risk for candidaemia. During the
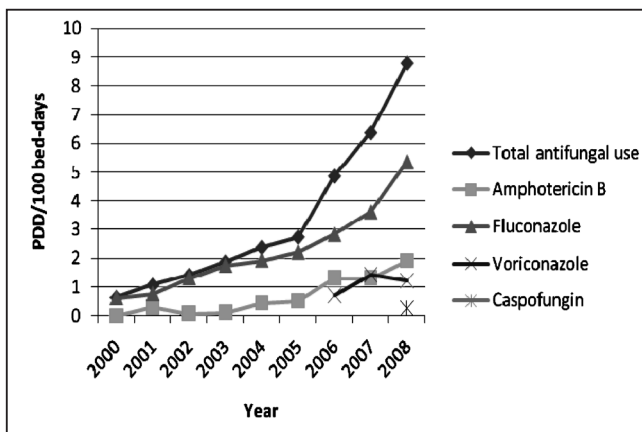
Table. MIC profile of *Candida* isolates to amphotericin B and % sensitivity to other antifungals tested					
Organism	Amphotericin B MIC <1 µg/ml	5 Flucytosine	Fluconazole	Itraconazole	Voriconazole
C. albicans	100	100	100	95	100
C. tropicalis	100	95	90.5	59	96.15
C. parapsilosis	100	95.5	66.1	64.7	91.6
C. glabrata	100	100	60.8	19.5	88.4
C. haemulonii	27.6	79.4	0	0	63.8
C. krusei	88.8	11.1	0	0	100
C. pelliculosa	100	42.8	57.1	28.5	100
Pichia ohmeri	100	100	40	40	100
C. rugosa	100	100	71.4	57.1	100
C. guilliermondii	100	100	75	50	100
C. utilis	100	40	100	40	100
C. famata	100	100	40	100	50
Candida lusitaniae	100	100	100	0	100
C. spp.[*]	93.7	81.2	37.5	25	80
Overall (all *Candida* isolates)	89.6	90.9	68.8	54.3	88.6

[*]*Candida* species not otherwise identified

same time period, in a separate analysis, we observed a significant increase in rate of antibacterial drug consumption in our institution which has doubled from 157.8 to 318.5 DDDs/100 bed days[22] (available from: *http//www.sgrh.com*). The observed increase in candidaemia was significant in ICU settings.

There has been a major increase in the prescription of antifungal drugs over the last two decades. In the present study, the overall antifungal use increased 13-fold between 2000 and 2008. As reported by others[16,23], fluconazole was the most frequently prescribed antifungal agent. Our hospital has high output liver, renal and bone marrow transplant units with 20,000 surgeries performed annually and as a result high fluconazole consumption as either presumptive/ prophylactic agent is observed.

The role of the widespread use of azoles in the shift to non-*albicans Candida* species has been largely debated and remains controversial. In the present study, there was a statistically significant correlation between yearly fluconazole use and increase in isolation of non-*albicans Candida* species, even though the antifungal susceptibility patterns revealed that the most common species *C. tropicalis* showed high sensitivity to fluconazole.

The new species *C. haemulonii*, previously known to cause an epidemic disease afflicting laboratory animals and onychomycosis in humans, has emerged as an opportunistic fungal pathogen that is capable of causing an outbreak of fungaemia[24]. *C. haemulonii* has shown increased MICs and resistance to both amphotericin B and fluconazole and also exhibited clinical failure[25]. Kim *et al*[26] reported the emergence of *C. haemulonii* from five Korean hospitals between 2004 and 2006, with genotyping results suggesting intra- and inter-hospital transmission of a clonal strain. Emergence of amphotericin B resistant *C. haemulonii* isolates is a matter of concern. This species was first isolated at our hospital in 2006 and its isolation increased significantly so that it became the third most common species isolated from 2006-2008.

Our susceptibility data showed that reduced susceptibility to fluconazole was common in *C. glabrata* and *C. parapsilosis*. Reduced susceptibility to fluconazole in *C. glabrata* was consistent with previously reported data[27,28]. In contrast, *C. parapsilosis* has usually been reported to be sensitive to azoles. However, Sarvikivi *et al*[29] have reported that the use of fluconazole prophylaxis contributed to the emergence of subclones of *C. parapsilosis* with decreased susceptibility among isolates responsible for BSI in

neonatal ICU. Similar findings were reported in an animal model[30]. Also, *C. parapsilosis* is known to form extensive biofilms on bioprosthetic materials such as central venous catheters (CVCs), which can confer relative resistance to antifungal agents.

Cross-resistance between fluconazole and voriconazole has been frequently reported in many species[31] and development of voriconazole resistance after fluconazole exposure without any known prior exposure to voriconazole has also been documented[6]. In our study, cross-resistance or reduced susceptibility to both fluconazole (MIC >16 µg/ml) and voriconazole was observed in 11.3 per cent isolates. These findings coupled with high azole consumption at our hospital may preclude the use of voriconazole as initial therapy in unstable patients with invasive candidiasis.

The present study has not addressed specific risk factors, which play a role in the selection of species causing fungaemia as well as variable susceptibility patterns. Moreover, this being a retrospective study, genotypic analysis of the isolates was not done, which could have ascertained clonality and epidemiology of spread of the various species especially *C. haemulonii*. This would have also helped in definitive identification of *Pichia ohmeri* isolates which are infrequently reported in literature. Also, species identification and antifungal susceptibility data were available only from 2006 and susceptibility testing was performed by recommended assays making exact comparisons difficult.

In conclusion, there has been a rise in the occurrence of candidaemia cases in our tertiary care hospital over the last decade. A significant epidemiological shift to higher isolation of non-*albicans Candida* species was noticed. The high usage of fluconazole appeared to have played a role in this shift, however, it may be recognised that other events like patient specific risk factors might have also contributed in selection of different species. Despite *C. tropicalis* being the commonest isolate, the emergence and increased isolation of amphotericin B and azole resistant *C. haemulonii* and the documentation of decreased susceptibility to fluconazole in *C. parapsilosis*, a species generally reported to be fluconazole sensitive, are a matter of concern. Decreased susceptibility to fluconazole with the threat of emergence of cross-resistance to voriconazole in the background of high azole consumption may limit the use of these agents as empirical therapy for *Candida* BSI before species identification and results of antifungal susceptibility testing are known.

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