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Prevalence and drug resistance pattern of *Candida species* in Pediatrics patients in Tertiary care hospital, North India

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Abstract

More than 17 species has been identified as causative agent of candidaemia. Identification of *Candida species* may help in selecting antifungal agents in severely ill ICU patients as the drug resistance continues to be a potential risk factor for cost effectiveness of treatment and outcome. This prospective study was conducted to identify the pattern of prevalence and drug resistance in *Candida species*. Total 60 isolates were identified and screened for drug resistance from ICU patients. Most commonly isolated species was *C. albicans* (41.66%) followed by *C. Tropicalis* (23.33%). Highest drug resistance was seen towards Itraconazole and Fluconazole. All *Candida* isolates remain susceptible to Voriconazole. Early diagnosis and prompt treatment can help in patient management and improve treatment outcome.

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Introduction

Candida bloodstream infections (BSIs) are a common cause of late-onset sepsis and are associated with substantial mortality, neuro developmental impairment, prolonged hospitalization in the intensive care unit (ICU) and represents an independent factor for predicting risk of death.[1-3] During last two decades increase in incidence of candidaemia have been noticed worldwide including India[4,5]

Candida albicans accounts for the majority of cases with candidaemia, but an increasing number of infections due to non-albicans spp. have been reported. According to the Surveillance and Control of Pathogens of Epidemiologic importance program, the most commonly isolated Candidanon-albicans was *C.glabrata* (causing 3%–35% of all candidaemia), followed by *C. Tropicalis*, *C. parapsilosis, C. krusei,* and other *Candida spp*. The SENTRY Antimicrobial Resistance Surveillance program reported that the rank order of the various Candidanon-albicans spp. differed among patients in various geographic locations, but the reason for such differences remains unclear. [6] Other studies also reported epidemiological data and risk factors regarding the development of nosocomial infection with certain *Candida* non-*albicans* spp. [7-9]

However, there is a relative scarcity of data regarding differences between Candida albicans and non-albicans bloodstream infections (BSI) in critically ill patients. For better outcome of therapy it is very important to know the species of *Candida* and the drug resistance pattern in the locality. We conducted this prospective study to understand geographical distribution and drug resistance pattern associated with BSI due to *Candida albicans* and *Candida* non-albicans spp. among critically ill patients.

Methods and Materials

The study was conducted in department of microbiology S.N Medical College Agra during Jan 2012 to Jan 2013. A total of 847 clinically suspected cases of septicemia were included in the study.

The blood culture was performed in the clinical laboratory of the hospital using standard protocols. The hands of the Health care workers, who had direct contact with patients, were cultured to rollout the contamination or carry over, by swabbing the interdigital areas and under their nails, using sterile swabs with Stuart medium. The reading was taken at the end of 48 hours. Demographic data includes age, gender and hospital unit. Intensive care units were categorized as follows: pediatric ICU and neonatal ICU.

Candidaemia was defined as at least one positive blood culture for *Candida spp*. in patients hospitalized for more than 48 h with signs or symptoms of infection. Patients with candidaemia were followed-up

Clinically for the treatment response after the microbiologically diagnosis until their discharge from the ICU or until the time of death. Cultures were considered negative if no growth occurred for 7 days. The phenotypic identification of the isolates of *Candida species* from the blood and hands of HCWs was done by the morphology of colonies, germ tube test, chromogenic medium (CHROMagar Hi media) and carbohydrate fermentation test. Further identification was carried out manually using the test of carbohydrate assimilation and on the basis of microscopic morphological features of the growth obtained in CMA via Dalmau Plate Culture technique. All isolates submitted as C. albicans with concordant colonial morphology on CHROMagar *Candida* were screened for growth at 42°C in order to differentiate possible C. dubliniensis isolates. [10] The cases were classified according to the responsible *Candida spp.* in the *C. albicans* and non-albicans candidaemia groups.

Antifungal susceptibility testing was performed for the following antifungal: Fluconazole, Itraconazole, Voriconazole, Amphotericin B, using CLSI guidelines.

The fungal strains were freshly sub-cultured on to SDA and incubated at 25° C for 3 days. The yeast isolates were suspended in sterile distilled water. 10 µl of slenderized suspension was inoculated onto the control plates. The plates were incubated at 25° C for 48 hours.

Result

Of the 847 Blood specimens processed 60 (07.08%) showed growth of *Candida species*. The patients included in this study were between new born and 18 years of age. Remaining 787 samples had other pathogen than *Candida species* either contamination/sterile.

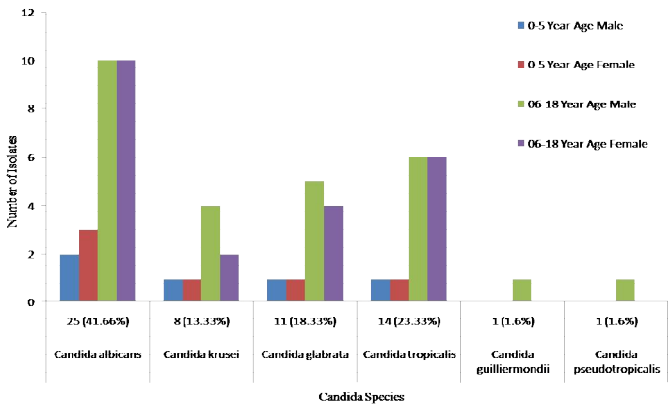
Distribution Pattern of Isolates between the Sexes

When the data from culture positive samples was organized as in Table 1 according to gender wise, it appeared that the overall prevalence of candidaemia in males was about 0.47% higher than females.

Table 1 Distribution Pattern of Isolates among the Sex and age.

Age	Male Examined	Male Positive for Candida (%)	Female Examined	Female Positive for Candida (%)	Total Number of Cases	Total Positivity %
0-5 Year	71	5	93	6	164	06.70%
06-18 Year	381	28	302	21	683	07.17%
Total Number of Cases	452	33	395	27	847	07.08%

Figure 1 shows distribution Pattern of Isolates between the Sexes and age. There was no specific pattern of isolates, when arranged according to sex and age wise. We could not associate any species correlation to any gender or any specific age group. Figure 1 Distribution Pattern of Isolates between the Sexes.



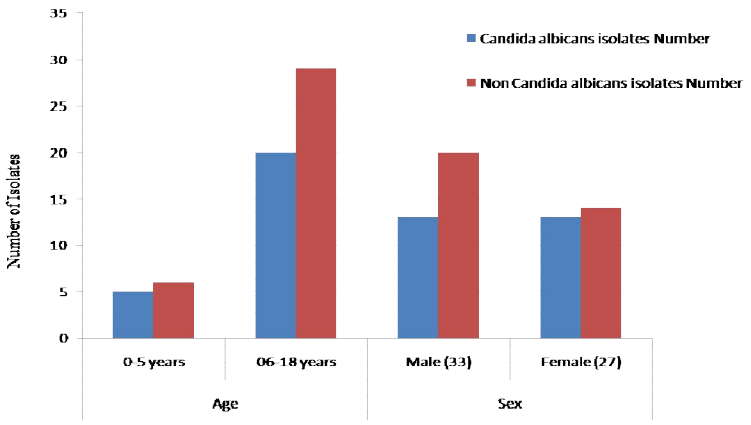
Drug resistance was detected in certain *Candida species* to a particular group of antifungal agents which is described in table 2

Table 2 Positivity according to time

Antifungal	Candida Species	Resistance	Sensitive
Amphotericin B	Candida albicans	04.00%	96.00%
	Candida krusei	00.00%	100%
	Candida pseudotropicalis	00.00%	100%
	Candida glabrata	00.00%	100%
	Candida tropicalis	00.00%	100.00%
	Candida guilliermondii	100.00%	NA
Itraconazole	Candida albicans	30.00%	70.00%
	Candida krusei	60.00%	40.00%
	Candida pseudotropicalis	15.00%	85.00%
	Candida glabrata	00.00%	100%
	Candida tropicalis	20.00%	80.00%
	Candida guilliermondii	00.00%	100%
Voriconazole	Candida albicans	00.00%	100%
	Candida krusei	00.00%	100%
	Candida pseudotropicalis	00.00%	100%
	Candida glabrata	00.00%	100%
	Candida tropicalis	00.00%	100%
	Candida guilliermondii	00.00%	100%
Fluconazole	Candida albicans	08.00%	92.00%
	Candida krusei	NA	NA
	Candida pseudotropicalis	00.00%	100%
	Candida glabrata	09.09%	90.90%
	Candida tropicalis	07.14%	92.85%
	Candida guilliermondii	0.00%	100%

The frequency of *Candida* non albicans species infection was more in age group of 06-18 years of male. We could not observe any relation of *Candida albicans* infection to a particular age or sex.

Figure 2 Distribution of *Candida albicans* and *Candida* non *albicans* gender wise and sex wise.



Discussion

According to published data till date the positivity of blood culture in Indian scenario varies from 03 % to 17% in north India. [11-13] More than 17 species of *Candida* have been implicated in human infections till date and the list of reported species continues to grow. *Candida species* has emerged as a new major pathogen in last two decades, accounting for 05.07- 18% [14-18] of total sepsis cases, which may be underestimated due to lack of multicentric studies.

Interestingly, we found higher prevalence rate of candidaemia in males 0.47% than female. We could not find any significant co-relation between *Candida species* to age wise or sex wise in our study. Although in Male of age group 06-18 years, *Candida* non albicans are more prevalent than the *Candida albicans.*

(Figure 1). Reason for this remains unclear. To establish this co relation much more study are required. In the recent reports there have been changes in the pattern of species prevalence and in the resistance pattern may be due to over use of antifungal agents.

Candida albicans (41.66%) was the most common species isolated from blood isolates in our study, followed by *Candida tropicalis* (23.33%), *C.glabrata* (18.33), *C.krusei* (13.33), *Candida guilliermondii* (1.60%), *Candida pseudotropicalis* (1.60%). Our data suggest predominance of Candida non albicans (58.33%) species over Candida albicans (41.66%), which is consistent with other published reports from northern part of India. Among the non-albicans *Candida species, C. tropicalis* alone stand for 40.00% of the infection. It has emerged as an important opportunistic pathogen. Similar reports have also been published by Adhikary et al. and Xess et al. from AIIMS, New Delhi. [17, 19-20]

Introduction of azoles, such as Fluconazole in the early 1990s, provided a new option for therapy against systemic fungal infections especially in critically ill patients.

The efficacy of Fluconazole in specialized adult populations has been documented for both the treatment and prevention of Candida infections. Because of acquired or intrinsic drug resistance in few *Candida species* against azoles, the *Candida species* pattern in ICUs have been changed. The increased use of Fluconazole has been determined to be the major cause of resistance towards it and predominance of non-albicans *Candida,* especially *C. tropicalis* over *C. albicans*. [21]

Amphotericin B and Voriconazole were the most promising drugs against the *Candida albicans* and Candida Non albicans species isolates in our study. Only one species *Candida albicans* showed resistance towards Amphotericin B 04.00%. Antifungal susceptible of Amphotericin B towards *C. guilliermondii* was not performed as it is intrinsic resistance to it. [21] None of the isolates were resistant towards Voriconazole. Voriconazole, Amphotericin B continues to show good efficacy. In resistance pattern of all *Candida* isolates, we could find the higher drug resistance towards Fluconazole and Itraconazole. Antifungal susceptibility of *C. krusei* for Fluconazole was not performed in our study as it is intrinsically resistant to it. [22] The decrease in susceptibility of Candida isolates to Fluconazole is a matter of concern as it is used for prophylactic agent. Isolates which showed resistance towards Fluconazole was *C. albicans* (08.00%), *C.glabrata* (09.09%) [23] and *C. tropicalis* (07.14%). 60% isolate of *C.krusei* were resistant to Itraconazole followed by C. albicans 30% C. tropicalis 20%.

This is an extremely disturbing trend, possibly associated with increased use of azoles as prophylaxis, especially in surgical units and intensive care units.

Conclusion

Infections with these yeasts also have a direct impact on the choice of empiric antifungal therapy and clinical outcome. Prior knowledge of species distribution in clinical isolates and drug sensitivity pattern among species help the clinician to choose early empirical therapy.

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