Original Research Article

Candidemia in intensive care units and their antifungal susceptibility pattern

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Abstract

Candida species are the commonest opportunistic fungal infections worldwide. The most common Candida species causing infection is *Candida albicans*. Candidemia is described as presence of candida species in bloodstream. It is a fatal fungal infection with mortality ranging from 35% to 75%. In ICU patients, the incidence varies from 0.24-34.3 patients per 1000 ICU admissions according to western literature. Antifungal susceptibility testing is a tool of increasing importance in clinical microbiological labs. The goal of AFST is to produce MIC values that may be used to guide patient therapy. **Objective:** Candidemia in intensive care units and their antifungal susceptibility pattern. **Materials and Methods:** Blood specimens from clinically suspected cases of BSI were processed by conventional blood culture or automated blood culture system as per availability. Blood from the bottles was subcultured on Sabouraud Dextrose Agar, antifungal susceptibility was performed on Candida isolates against antifungal drugs by broth microdilution. **Results:** A total of 1816 patients of suspected BSI were admitted in the ICUs during the study period. 75 of these samples were positive for growth of Candida species. Candidemia among males and females was almost equal. Commonest non-albicans species isolated were *C. tropicalis*. Posaconazole and flucytosine are the two most susceptible antifungal drugs for all the isolated candida species. **Conclusion:** Antifungal susceptibility plays an important role in targeted therapy of infection caused by common and uncommon Candida species. This will help to prevent emerging antifungal resistance and thereby reduce patient morbidity and mortality.

Keywords: candidemia, antifungal susceptibility, non albicans candida, candida tropicalis

Introduction

Candida species are the commonest opportunistic fungal infections worldwide (1). They are generally a part of normal microbial flora of skin and mucous membrane in immunocompetent persons (2). But in critically ill patients with underlying disease like diabetes mellitus and in immunocompromised patients they may lead to fatal systemic infections (2). Nearly 200 Candida species are known till date among which 10% cause infections in humans. The most common Candida species causing infection is *Candida albicans* (3).

Candidemia is described as presence of candida species in bloodstream. It is a fatal fungal infection with mortality ranging from 35% to 75% (4). The occurrence of candidemia is on a rise worldwide (5). Of all blood stream infections (BSI), yeasts belonging to genus Candida are amongst the top 10 microorganisms (6). In ICU patients, the incidence varies from 0.24-34.3 patients per 1000 ICU admissions according to western literature(7).

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Antifungal susceptibility testing is a tool of increasing importance in clinical microbiological labs. The goal of AFST is to produce MIC values that may be used to guide patient therapy, inform epidemiological studies and track rates of antifungal resistance. As more therapeutic choices became available the value of detecting antifungal resistance and the need for optimization of antifungal choice increased (8).Although *C. albicans* remains the commonest species, there has been a shift towards non-albicans species(9). Emergence of newer Candida species have a greater propensity for nosocomial infections and are increasingly being reported as multi drug resistant in ICUs (10). Although some Candida species are inherently resistant to antifungals, there are increasing reports of reduced susceptibility of Candida species to commonly used antifungals (11,12). This can be due to formation of biofilms which diminish accessibility of the antifungal, selection of spontaneous mutations that increase expression or decreased susceptibility of target, altered chromosomal abnormalities, overexpression of multidrug efflux pumps and the ability to escape host immune defence (13).In view of this, the present study was carried out in a tertiary care hospital with the objective to find out the prevalence of candidemia among patients admitted in intensive care units (ICU) and

with their antifungal susceptibility pattern for azoles, polyenes, flucytosine and caspofungin.

Materials and Methods

A prospective, observational study was conducted for a period of 1 year after approval by the Institutional Ethics Committee (IEC). The samples included all clinically suspected cases of bloodstream infections (BSIs) in intensive care unit (ICU) patients which included medical intensive care unit (MICU), surgical intensive care unit (SICU), paediatric intensive care unit (IPCU) and neonatal intensive care unit (NICU). Blood specimens from clinically suspected cases of BSI were processed by conventional blood culture or automated blood culture system as per availability. For further mycological investigations, blood from the bottles was subcultured on Sabouraud Dextrose Agar (SDA) with chloramphenicol slants and incubated at 30°C and 37°C. Candida species usually grows as white, pasty colonies on SDA slants. The candida species were identified and speciated, using standard conventional methods such as Gram's staining, germ tube test, growth on CHROM agar, urease test, sugar assimilation tests and Dalmau culture method. Inspite of these tests, if the identity of a Candida species remained inconclusive, they were subjected to automated method – VITEK 2 TM identification system(bioMerieux).Antifungal susceptibility was performed on Candida isolates against fluconazole, flucytosine, posaconazole, voriconazole, caspofungin, amphotericin B and itraconazole by broth microdilution using CLSI M27-A3 and CLSI M27-A4 document(14,15).

Results

A total of 1816 patients of suspected BSI were admitted in the ICUs during the study period. Blood cultures of all these patients were received for microbiological investigation. 75 of these samples were positive for growth of Candida species (4.12%). Of these 75, 35 (1.92%) were adults, 21 (1.15%) were children and 19 (1.05%) were neonates. Candidemia among males and females was almost equal. Highest number of samples were received from MICU (552,30.39%) followed by NICU (477,26.27%), IPCU (432,23.79%) and SICU (355,19.55%).SICU had the highest candidemia rate of 5.91% followed by IPCU (3.93%), NICU (3.56%) and MICU (3.62%).12 (16%) of the isolated Candida were *Candida albicans* whereas the remaining 63 (84%) belonging to non-albicans group.

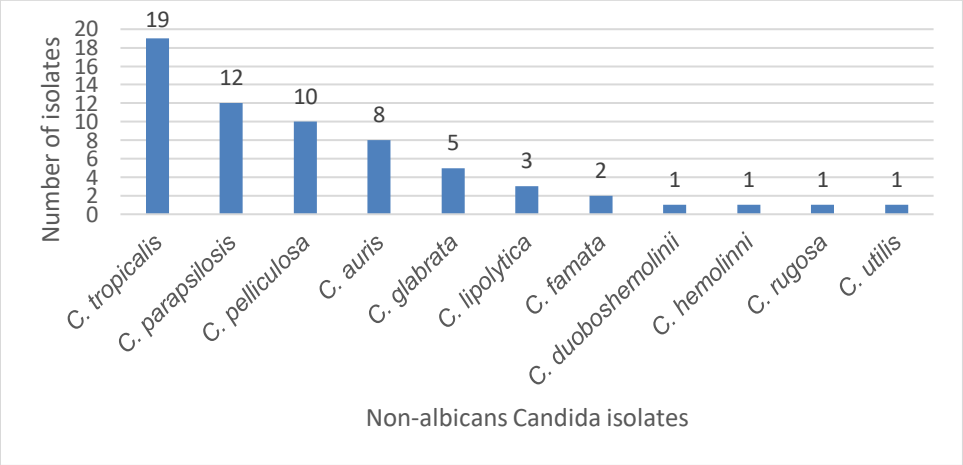

Fig 1: Distribution of Non-albicans Candida species (n=63)

Commonest non-albicans species isolated were *C. tropicalis* 19 (30.15%) followed by *C. parapsilosis* 12 (19%) and *C. pelliculosa* 10 (15.87%). *C. auris* was also found in 8 patients (12.69%).

Table 1: Candida species isolated from different ICUs (n=75)

Organism	MICU (20)	SICU (21)	NICU (17)	PICU (17)
C.albicans	4	2	4	2
C.auris	2	3	3	0
C.duobushaemulonii	1	0	0	0
C.famata	0	0	2	0
C.glabrata	1	1	1	2
C.haemulonii	1	0	0	0
C.lipolytica	1	1	0	1
C.parapsilosis	5	2	3	2
C.peliculosa	0	2	2	6
C.rugosa	1	0	0	0
C.tropicalis	4	9	2	4
C.utilis	0	1	0	0

19 isolates of *C.tropicalis* followed by 12 isolates of *C. albicans* and *C. parapsilosis* each, followed by 10 isolates of *C. pelliculosa* and 8 isolates of *C. auris* were the commonest isolates recovered from patients in MICU, SICU, NICU and IPCU. *C.parapsilosis* was most frequently isolated from MICU, *C.tropicalis* from SICU, *C.albicans* from NICU and lastly *C.pelliculosa* from PICU.

Table 2 A: Antifungal susceptibility of *C. albicans* and non-albicans Candida species (Susceptibility to azoles)

	Susceptibility to anti-fungal Drugs								
	Fluconazole			Voriconazole		Posaconazole		Itraconazole	
	S	SDD	R	S	R	S	R	S	R
***C. albicans* (n=12)**	9	1	2	10	2	12	0	10	2
%	75	8.3	16.7	83.3	16.7	100	0	83.3	16.7
Non-albicans Candida									

***C. glabrata* (n=5)**	1	0	4	5	0	5	0	1	4
%	20	0	80	100	0	100	0	20	80
***C. parapsilosis* (n=12)**	10	2	0	12	0	12	0	10	2
%	83.3	16.7	0	100	0	100	0	83.3	16.7
***C. tropicalis* (n=19)**	16	0	3	18	1	19	0	16	3
%	84.2	0	15.8	94.7	5.3	100	0	84.2	15.8

Table 2 B: Antifungal susceptibility of *C. albicans* and non-albicans Candida species (Susceptibility to flucytosine, amphotericin B and caspofungin)

	Susceptibility of anti-fungal Drugs						
	Flucytosine		**Amphotericin B**		**Caspofungin**		
	S	**R**	**S**	**R**	**S**	**I**	**R**
***C. albicans* (n=12)**	12	0	11	1	11	0	1
%	100	0	91.7	0	91.7	0	8.3
Non-albicans Candida							
***C. glabrata* (n=5)**	5	0	4	1	2	2	1
%	100	0	80	20	40	40	20
***C. parapsilosis* (n=12)**	12	0	12	0	12	0	0
%	100	0	100	0	100	0	0
***C. tropicalis* (n=19)**	19	0	18	1	17	1	1
%	100	0	94.7	5.3	89.4	5.3	5.3

Posaconazole and flucytosine are the two most susceptible antifungal drugs for all the isolated candida species.This is followed by voriconazole having a high susceptibility for all candida species, between 83.3% to 100%. Fluconazole and itraconazole both show variable susceptibility, both are least effective for *C.glabrata.* Polyenes like amphotericin B also show good susceptibility to both candida albicans and non-candida albicans species ranging between 80% to 100%.Lastly echinocandins like casfungin is least susceptible for *C.glabrata* and most for *C.parapsilosis*.

Discussion

Critically ill patients admitted in ICUs have a predisposition towards developing candidemia(16). Weakened host immune mechanism, presence of various indwelling medical devices, prolonged hospital stay and long term use of antimicrobials in the ICUs alter the normal microbial flora of these patients thereby exposing them to greater risk of invasive infections by *candida* (16). Resistance to antifungal agents is on the rise. The potential clinical importance of species-level identification has also been recognized. Candida species are known to differ in expression of various virulence factors and antifungal susceptibility. The rising incidence of NAC isolates in the immunocompromised patients and the emergence of antifungal resistance, necessitates the judicious use of antifungal prophylaxis. Characterization and sensitivity profiles of locally prevalent Candida strains and the knowledge of risk factors for invasive candidiasis can help in deciding clinical strategies(17)In the present study, the prevalence of candidemia in NICU was 3.56%. Basu *et al.* (3.64%) (18), Goel *et al.* (19) and Shrivastava *et al.* (20) have reported a higher prevalence of 8.10% and 6.95% respectively. Juyal *et al.* (21) and Yunus *et al.* (22) have also reported higher rates (24.08%, 15.70%) of neonatal candidemia. Neonates have an underdeveloped immune system which predisposes them to various nosocomial infections including candidemia (18). Lower rate of candidemia among the neonates in the present study could be due to better level of new born care in the NICU. There was no marked difference in the prevalence of candidemia in IPCUs in various studies. Prevalence of candidemia in IPCUs in the present study (3.93%) was comparable with other studies (9,23,24).In the present study, the prevalence of candidemia in SICU was 5.91%. In majority of other studies, high levels of prevalence of candidemia were noted in SICUs ranging from 14.95% to 21.90% (25–27). However, prevalence of candidemia was comparatively high in SICU as compared to other ICUs in the present study. Candida being a normal commensal of the gastrointestinal tract, might get access to the bloodstream during surgical procedures due to disruption of the mucosal lining. Therefore, surgery is considered an independent risk factor for candidemia.Non-albicans Candida species among candidemia isolates is a constant threat to public health. In the present study, a total of 75 isolates of Candida were identified and they were speciated. 16% of these were *C. albicans* whereas remaining 84% belonged to non-albicans Candida species. Chakrabarti *et al.* (28) in their study identified 20.1% isolates as belonging to *C. albicans* and remaining 79.1% belonged to non-albicans. Debahuti *et al.*(29) had 70% non albicans Candida isolates in their candidemia patients. Similarly Giri *et al.* (5) and Tejan *et al.* (10) in their studies found the prevalence of non-albicans Candida species at 10.25% and 79.16% respectively. Similar studies done by Shivaprakasha *et al.* (30) (96.6%), Rani *et al.* (31) (96%), Tak *et al.* (25) (86.3%) and Pahwa *et al.* (32) (82.7%) also found higher prevalence of non-albicans species among BSI due to Candida species. A shift to higher isolation of non albicans candida species was observed during 1991 to 1995 this maybe due increased use of invasive devices, broad spectrum antibiotic agents, more extensive surgical procedures and use of advanced life support on various transplant patients (33). Prophylactic use of routine antifungals has been postulated to be causing the shift to non-albicans candidemia.

C. tropicalis was the commonest non-albicans isolate in all the studies including the present one. Chakrabarti *et al.* (28) reasoned that horizontal transmission and compromise of infection control systems were distinct possibilities for high rate of *C. tropicalis* in various studies.There was not much significant difference in the percentage isolation of *C. glabrata* and *C. parapsilosis* between the present study and the other studies (5,9,25,28,29,34)The frequency of *C. auris* (10.67%) *and C. pelliculosa* (13.33%) were higher in the present study in comparison to other studies (9,28,34). This suggests changing epidemiology of Candida species causing infections in our set up and necessitates strengthening of infection control practices. Concern about the emergence and spread of *Candida auris* as cause of invasive infection in hospitals stems from 3 characteristics of this opportunistic pathogen – 1) resistance to various antifungal drugs, 2) horizontal transmission among hospital patients causing nosocomial outbreaks and 3) high associated death rates.It was observed that the spectrum of Candida species differs among all ICUs in our setting. In MICU, predominant Candida species isolated was *C. parapsilosis* (25%). However, in SICU, NICU and PICU, the predominant species were *C. tropicalis* (42.85%), *C. albicans* (23.52%) and *C. pelliculosa* (35.29%) respectively.

This has also been observed in other studies and there is a marked difference in the species isolated in respective ICUs. This might be due to difference in the local epidemiology and factors prevalent in different set ups (18–20,23–27,35–37).There was variable susceptibility of *C. albicans* and non-albicans Candida to seven antifungal agents tested in the present study (Table 2A,2B). This susceptibility pattern was also observed by Chakrabarti *et al.*,, Adhikary *et al.*,Tejan *et al.*and Nurul *et al.*Although flucytosine has 100% susceptibility, side effects associated with it renders its use rare

and mostly in combination therapy. There is an impending threat of increasing resistance to azoles, which may be attributed to them being used for prophylaxis and empiric use in invasive infections.

Conclusion

The present study highlights the prevalence of candidemia due to non albicans candida species among suspected cases of BSI in ICU patients in a tertiary care hospital. Routine screening of BSIs for candidemia is done and when detected a complete ID and AFST is essential for appropriate management of the patients. Antifungal susceptibility plays an important role in targeted therapy of infection caused by common and uncommon Candida species. This will help to prevent emerging antifungal resistance and thereby reduce patient morbidity and mortality.

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