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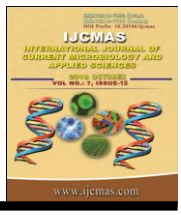

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Antifungal Susceptibility Profile of Candida Isolates from Bloodstream Infections in Hospitalised Patients at Tertiary Care Hospital

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A B S T R A C T

During recent decades, there has been a change in the epidemiology of Candida infections, characterized by progressive shift from predominance of *Candida albicans* to non albicans Candida. The aim of present study to isolate and identify the different Candida spp. from BSIs and evaluate its antifungal susceptibility pattern the present study was conducted in department of Microbiology for a period of one year (January - December 2016) which included, 48 Candida spp. isolated from BSIs. The speciation was done by conventional methods. Antifungal susceptibility testing of the isolates was performed by Minimum Inhibitory Concentration test. A total of 48 isolates of Candida species were recovered from blood samples of 454 patients [*Candida albicans* (31.25%), *C. tropicalis* (25%), *C. glabrata* (20.84%), *C. krusei* (16.66%), *C. parapsilosis* (4.17%), *C. guilliermondii* (2.08%)]. Isolation of NAC spp. was significantly higher than *Candida albicans*. Fluconazole and Amphotericin B resistance was seen in 18 (37.5 %) and 3(6.25%) of the isolates respectively. Candidemia is emerging as a significant problem in hospitalized patients. Non albicans candida is major cause of candidemia as found in our study.

Introduction

The frequency of invasive, opportunistic mycosis has increased significantly over the past two decades. Candida species account for 8-10 % of all nosocomial blood stream infections (Pfaller *et al.*, 2006). Increased incidence of candidemia is seen in hospitalised patients especially admitted in Intensive care units (ICUs). It is reported as the 4th common cause of blood stream infections (BSIs) in USA, with a mortality rate as high as 30-40 % (Beck-Sague and Jarvis, 1993). This is directly related to the increasing number of patients at risk of serious fungal infections, including patients undergoing blood and marrow transplantations, solid organ transplantation, major gastrointestinal surgery, neoplasia, patients with acquired immunodeficiency syndrome, on immunosuppressive therapy (Gudlaugsson *et al.*, 2003).

Low birth weight, central venous catheter, urinary catheter, mechanical ventilation, premature infants, diabetes, prolonged use of broad spectrum antibodies also several other predisposing factors are responsible for the occurrence of Candidemia in ICUs (Pfaller

and Diekema, 2007). Recent report suggests a shift in distribution of Candida species from *Candida albicans* to non albicans candida in cases of candidemiz (Rex *et al.*, 1995).

The prospective antifungal therapy alliance (PATH) study by Pfaller *et al.*, between 2004 and 2008 reported an increased incidence of 54.4% of non albicans candida (Pfaller *et al.*, 2014). Increased incidence of antifungal drug resistance has major cause of concern in management of Candidemia (Sahni *et al.*, 2005). The aim of present study was to speciate Candida isolates from blood cultures, & to evaluate the antifungal susceptibility pattern in these isolates will help in early diagnosis & prompt therapeutic intervention.

Materials and Methods

This study was carried out in the department of Microbiology, Dr. P.D.M.M. College & Hospital, Amravati, a tertiary care center in Maharashtra during the period January 2016 to December 2016.Ethical clearance for the study was obtained from the Institutional Ethics Committee.

Blood samples were collected aseptically in Brain Heart Infusion (BHI) broth from suspected cases of Blood stream infections in different wards and ICUs.

The BHI bottle was incubated at 37ºC in the laboratory. Subculture was performed after 48 hours and on 7th day before being reported negative. Subculture was performed on Blood agar, MacConkey agar. Colonies of yeast on Blood agar were identified by their smooth creamy coloured appearance and Gram's staining and subcultured on Sabouraud's Dextrose Agar medium. Speciation of Candida was done by assessing Germ tube test, assimilation and fermentation of sugars, Chlamydospore formation on corn meal agar, colony colour on Hichrom Candida agar.

Antifungal susceptibility testing of the isolates was performed by Hicomb MIC test (Himedia Laboratories Mumbai). The antifungal agents used were Amphotericin B (range 0.002-32 mcg), Fluconazole (range 0.016-256 mcg), Itraconazole (range 0.002-32 mcg), Ketoconazole (range 0.002-32 mcg) and Voriconazole (range 0.002-32 mcg).

The suspension of the isolate to be tested was prepared in 0.85% saline. The turbidity of each suspension was adjusted to 0.5 Mc Farland standard. The suspension was inoculated on agar plates containing RPMI 1640 supplemented with glucose using sterile cotton tipped swab. The antifungal strips were placed on the media and the plates were incubated for 48 h at 35ºC. The minimum inhibitory concentration (MIC) of each isolate against each antifungal tested was read after 24 and 48 hr.

C. albicans ATCC 90028 and *C. parapsilosis* ATCC 22019 were used for the purpose of quality control. The antifungal susceptibility of the isolates was reported as sensitive (S), dose dependent-susceptible (DDS) and resistant (R). For Fluconazole and Itraconazole the results were evaluated as per the interpretive susceptibility criteria recommended by Clinical and Laboratory Standard Institute (CLSI) [formerly known as National Committee for Laboratory Standards (NCCLS)] M27-A2 standard guidelines. (Clinical and Laboratory Standards Institute, 2002) Due to the lack of defined breakpoints for amphotericin B and ketoconazole, arbitrary values based on the studies of other researchers were used (Priscilla *et al.*, 2002).

Results and Discussion

In the present study, between January to December 2016, out of 454 blood culture samples, Candida spp. were isolated from the blood cultures of 48 patients. Figure 1 shows

the Age and sex distribution of Candidemia patients. Male predominance was noted in our study (n= 31/48) 64.6%. Candidemia was common in below 10 yrs and more than 50 yrs age groups in males than females. In this study predominant isolates were NAC spp. 33 (68.75) and *C. albicans* was isolated from 15 (31.25 %) cases (Table 1). Among the NAC species, *C. tropicalis*, *C. glabrata* and *C. krusei* were the major isolates (Figure 2).

The most important risk factors associated with candidemia was ICU stay, followed by Neonates, Catheter related infections, Diabetes (Figure 3).

The antifungal susceptibility and resistant pattern of all Candida isolates from blood stream infections was evaluated (Table 2).

A total of 18 (37.5%) isolates were resistant to Fluconazole. Fluconazole resistant was more in *C. tropicalis* followed by *C. glabrata* (Figure 4).

Maximum resistance to Ketoconazole was shown by *C. albicans* followed by *C. tropicalis* and *C. glabrata* (Figure 5). Itraconazole resistance was more in C. tropicalis (Figure 6). Voriconazole resistant was also noted in 3 (6.25%) and Amphotericin B resistant was noted in 3 (6.25 %) was shown in figure 7 and 8 respectively. Resistant to Amphotericin B and Voriconazole was not noted in *C. guillermondii* and *C. parapsilosis.*

The prevalence of *Candida* species in BSI has increased worldwide in the last three decades. In our study overall prevalence of Candida species in BSI of ICU patients was found to be 10.57% in the one year study period.

There are many reports on the prevalence of Candida in BSI from different part of the world. In the United States, a seven yearlong study has reported Candida species to be the 4th most common cause of BSI in hospitals (Wisplinghoff *et al.,* 2004). A 10 year study on the epidemiology of Candidemia in Switzerland found Candida species to be the 7th most common cause of BSI in tertiary care hospital (Marchetti *et al.,* 2004).

Lot of variation in the prevalence and incidence of Candidemia have been reported from India. A study by Verma *et al.,* from SGPGI, Lucknow ranked *Candida* species as 8th among all isolates causing BSI with incidence rate of 1.61% (Verma *et al.,* 2003). In a five year study from All India Institute of Medical Sciences (AIIMS), New Delhi, Xess *et al.,* found a prevalence of 6 % for Candida Species in BSI (Xess *et al.,* 2007). Sahni *et al.,* from Maulana Azad Medical College, New Delhi found the incidence rate of Candidemia to be 6.9 % (Sahni *et al.,* 2005).

Another New Delhi based study found that the percentage of Candida species among positive blood culture isolates was 18% (Kothari and Sagar, 2009). Kumar *et al.,* from South India reported an incidence rate of 5.7% for Candidemia among children with onco-haematological malignancies. (Kumar *et al.,* 2005) Another study from Rohtak, North India reported an isolation rate of 8.1% for Candida species from cases of neonatal septicaemia (Goel *et al.,* 2009). A study by Jain *et al.,* during year 2001 showed Candidemia to be present in 6% of neonates with suspected septicaemia (Jain *et al.,* 2003) and during year 2003 Candida was isolated from a total of 90 neonates i. e. isolation rate 13.6 % where majority of the isolates were non albicans Candida (Jain *et al.,* 2004). Prateek *et al.,* North India reported prevalence of 16% for Candida species in BSI (Gupta *et al.,* 2015). A Two year study from SCB Medical college, Cuttack M. Bhatt *et al.,* found a prevalence of 9.4% for *Candida* sp in BSI (Bhatt *et al.,* 2015) and Giri *et al.,* reported prevalence of 0.65% (Giri *et al.,* 2013) (Table 3).

Table.1 Comparison of antifungal susceptibility of *C. albicans* & non-albicans

Isolates	Number %	Resistance %				
	N=48	Fluconazole	Ketoconazole	Voriconazole	Itraconazole	Amphotericin B
C. albicans	15 (31.25%)	4 (26.66 %)	4 (26.66 %)	1 (6.66 %)	2 (13.33 %)	0 (0 %)
Non albicans Candida	33 (68.75%)	14 (42.42 %)	10 (30.30 %)	2 (6.06 %)	9 (27.27 %)	3 (9.09 %)

Table.2 Antifungal resistance pattern of Candida species

Candida species	No. of cases (n=48)	Resistance %				
		Fluconazole	Ketoconazole	Voriconazole	Itraconazole	Amphotericin B
C.albicans	15	4 (26.66%)	4 (26.66%)	1 (6.66%)	2 (13.33%)	0 (0%)
C. tropicalis	12	5 (41.66%)	4 (33.33%)	0 (0%)	4 (33.33 %)	1 (8.33%)
C. glabrata	10	4(40%)	3 (30%)	1(10%)	3 (30%)	1 (10%)
C. krusei	8	3 (37.5%)	2 (25 %)	1 (12.5%)	1 (12.5 %)	1 (12.5%)
C. parapsilosis	2	1 (50%)	1 (50%)	0 (0%)	1 (50 %)	0 (0%)
C. guilliermondii	1	1 (100 %)	0 (0 %)	0 (0%)	0 (0%)	0 (0%)
Total	48	18 (37.5 %)	14 (29.16 %)	3 (6.25%)	11 (22.91%)	3 (6.25%)

Table.3 Showing Indian studies on Fluconazole, Itraconazole, Voriconazole resistance

Reference	Place of study	Percentage resistance to azoles
Present study, 2017	Amravati, Maharashtra	Fluconazole (37.5) Itraconazole (22.91) Voriconazole (6.25)
Kothari *et al.*, 2008	New Delhi	Fluconazole (36) Itraconazole (24) Voriconazole (56)
Xess *et al.*, 2007	New Delhi	Fluconazole (11.7)
Gupta *et al.*,2001	New Delhi	Fluconazole (37.5)
Capoor *et al.*, 2005	New Delhi	Fluconazole (4.9) Itraconazole (3.9)
Kumar *et al.*, 2005	Chennai	Fluconazole (17.2)
Goel *et al.*, 2009	Rohtak	Fluconazole (4.5)
Adhikary *et al.*, 2011	Banglore	Fluconazole (25)
Kaur R *et al.*, 2014	New Delhi	Fluconazole (58.25)

Fig.1 Age and sex distribution of Candidemia patient

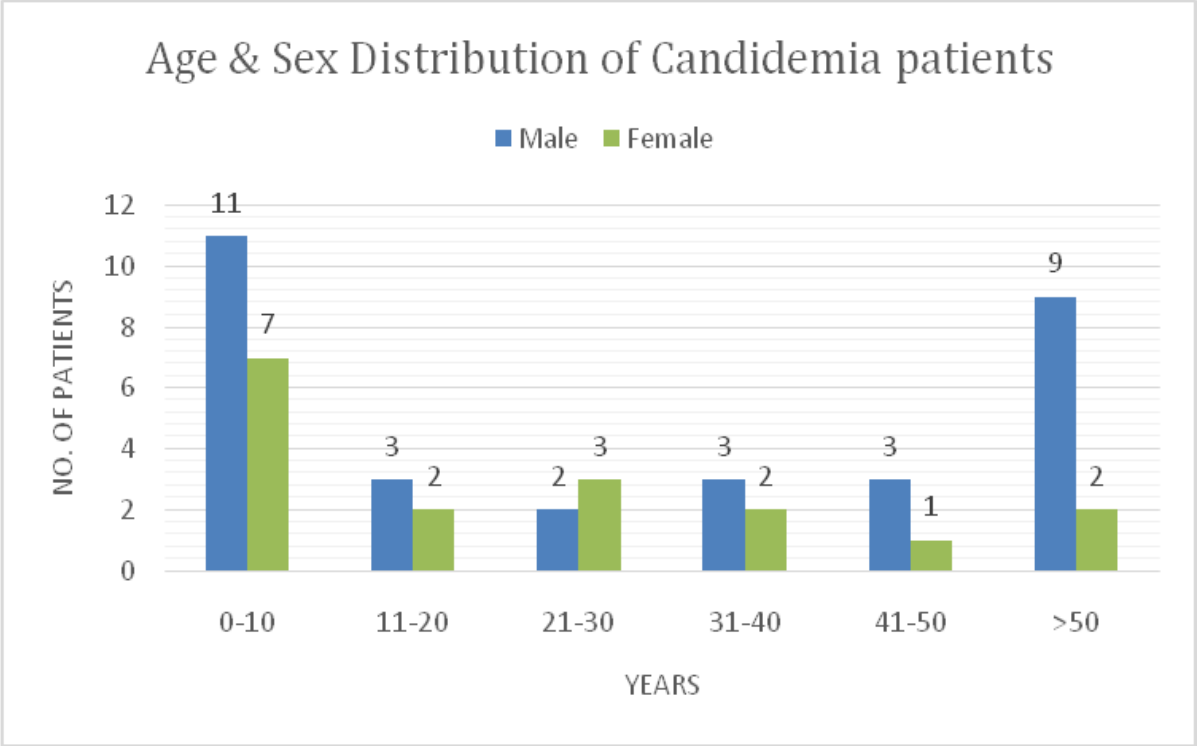


Fig.2 Distribution of *Candida* species isolated from Candidemia patients

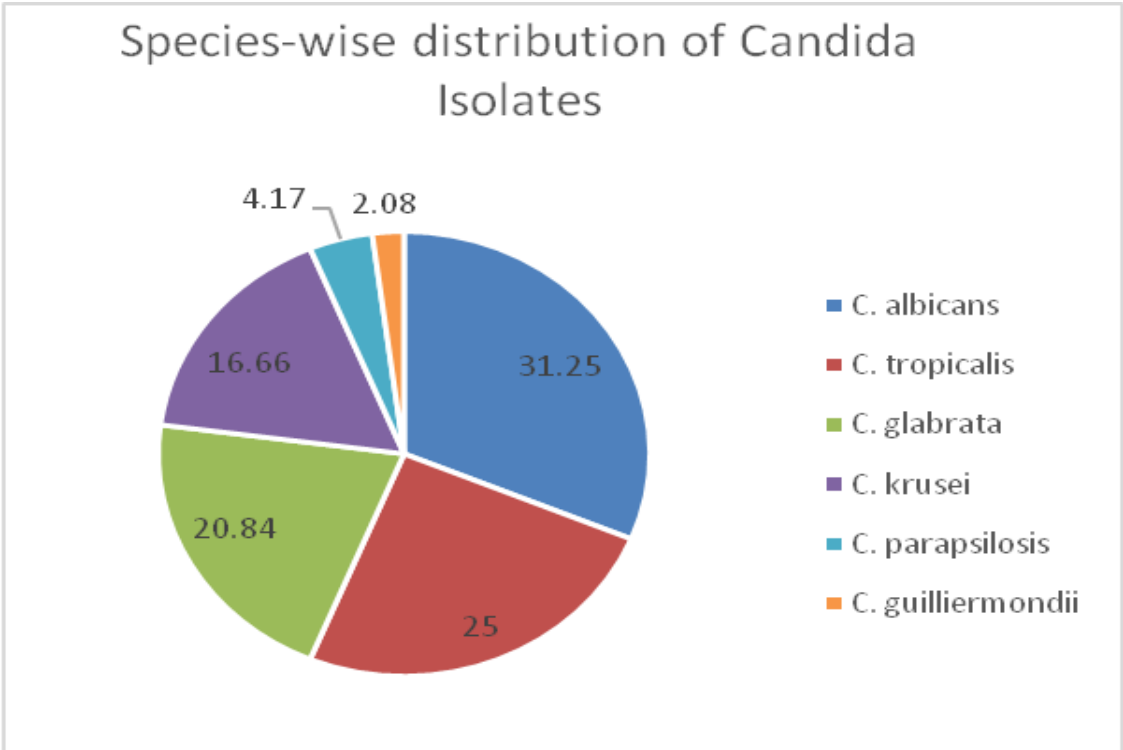


Fig.3 Risk factors predisposing Candidemia

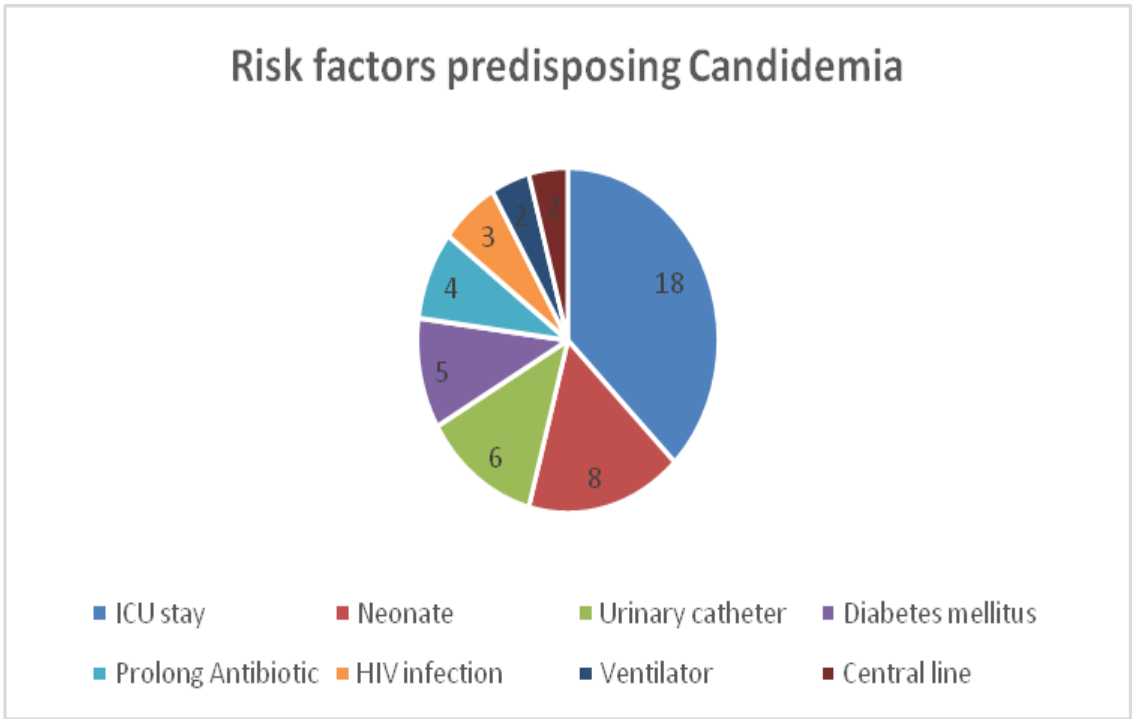


Fig.4 Antifungal profile of *Candida albicans* & NAC Spp (Fluconazole)

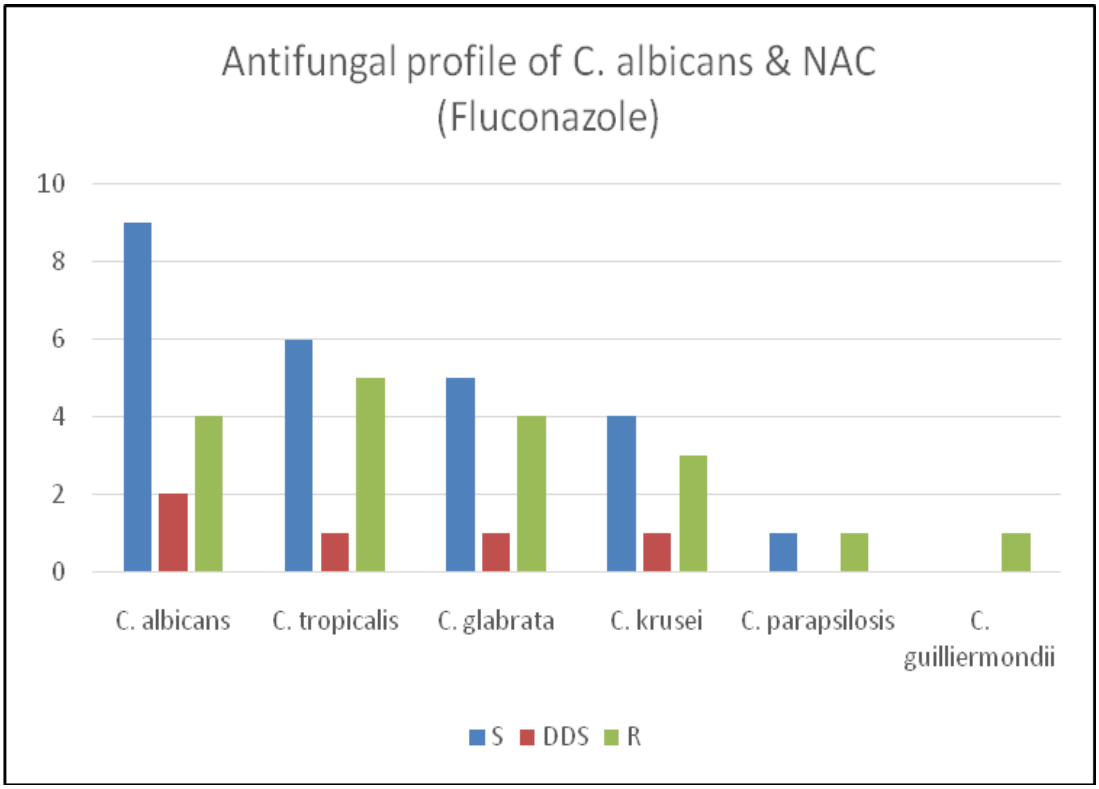


Fig.5 Antifungal profile of *Candida albicans* & NAC Spp (Ketoconazole)

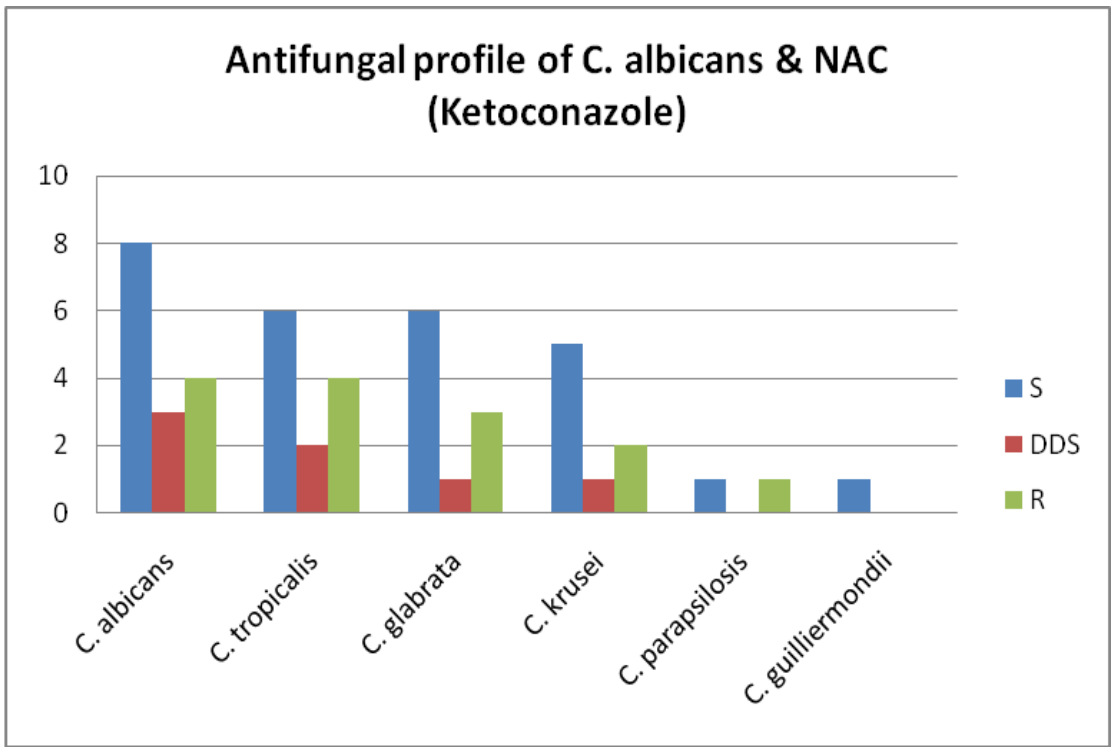


Fig.6 Antifungal profile of *Candida albicans* & NAC Spp (Itraconazole)

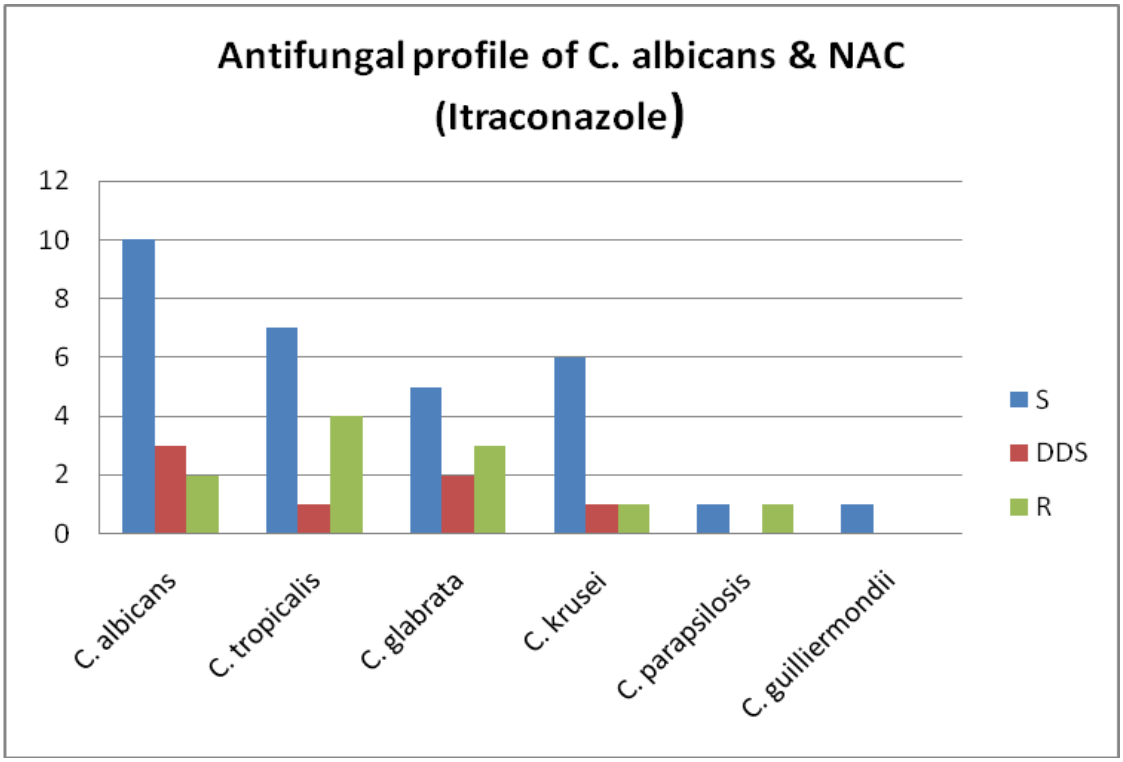


Fig.7 Antifungal profile of *Candida albicans* & NAC Spp (Voriconazole)

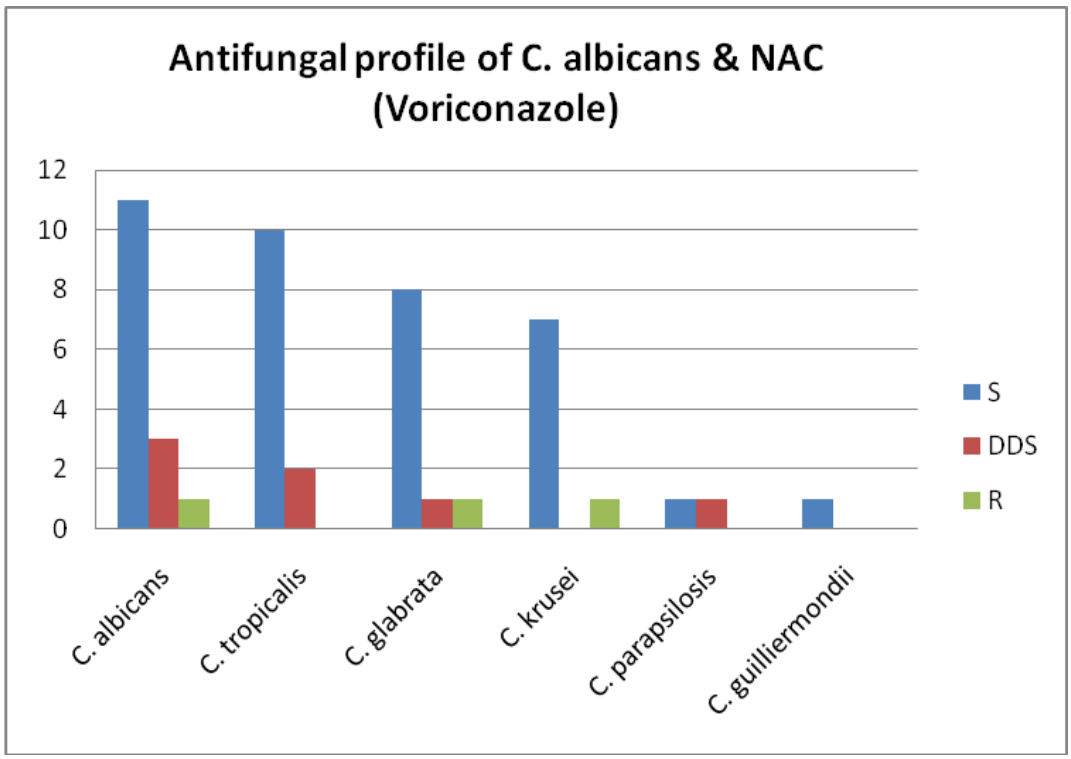
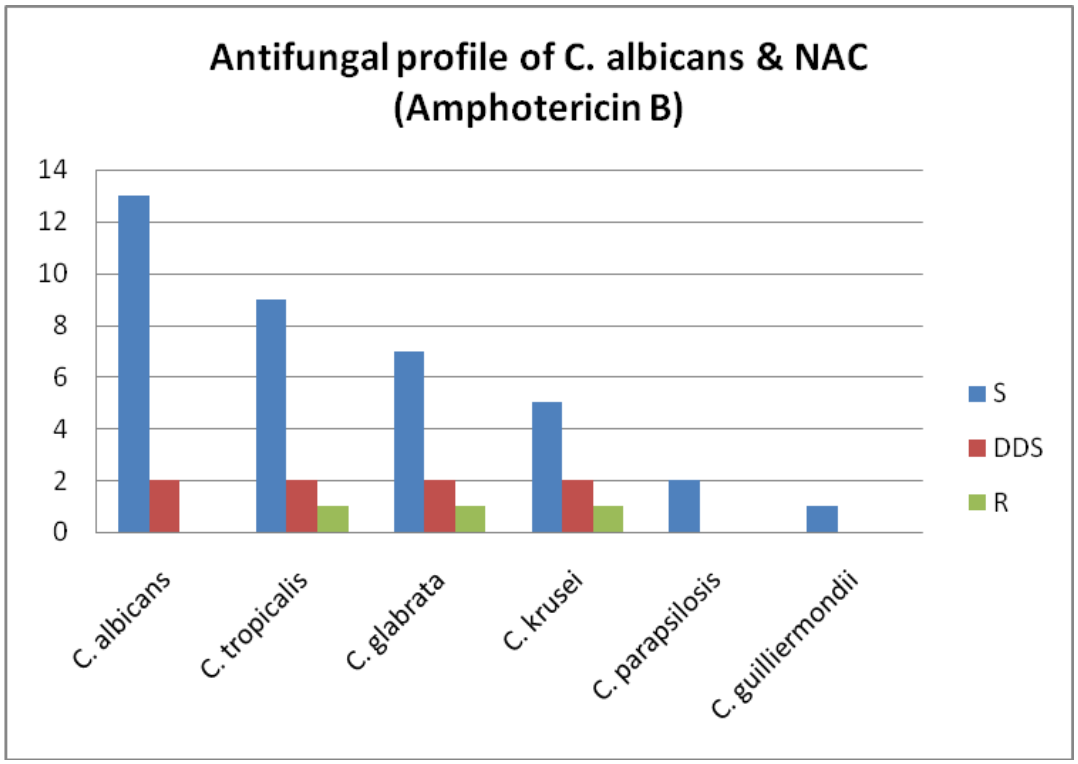


Fig.8 Antifungal profile of *Candida albicans* & NAC Spp (Amphotericin B)



The incidence of BSI caused by NAC spp. was higher than *C. albicans* at our hospital. Among the NAC spp. *C. tropicalis* followed by *C. glabrata* and *C. krusei* pre-dominantely caused BSI. A number of international surveillance programs like ARTEMIS Antifungal Surveillance study conducted in 127 heath care centres in 39 countries have documented increased prevalence of NAC species like *C. tropicalis* and *C. parapsilosis* (Pfaller *et al.,* 2005).

C. tropicalis was found to be the most common isolates from Candidemia pts by (Shivprakash *et al.,* 2007) (35.6%) and (Adhikary *et al.,* 2011) (39.7%) respectively. Xess *et al.,* from AIIMS, New Delhi also found *C. tropicalis* to be the most common species of Candida in blood isolates (35.3 %) (Xess *et al.,* 2007).

Factors like increased use of antifungal drugs, use of broad spectrum antibiotics, long term use of catheters, and increased in number of immunocompromised patients contributes to the emergence of *C. tropicalis* (Kothavade *et al.,* 2010), previous studies by Chakraborti *et al.,* (2009), Singh *et al.,* (2011) and Tak *et al.,* (2014) are in agreement with our study.

C. glabrata was the second most common NAC spp isolated in the present study. Trick *et al.,* also Chander *et al.,* reported a considerable increase in the incidence rate of isolation of *C. glabrata* from BSI pts (Trick *et al.,* 2002; Chander *et al.,* 2013). *C. glabrata* infections are common in immunocompromised hosts and diabetes mellitus patients. It is also associated with high mortality rates in at risk hospitalised and immunocompromised patients (Hitchcock *et al.,* 1993).

In recent years, emphasis has been laid on other risk factors like long period of hospitalization in ICUs especially surgical ICUs (Blumberg *et al.,* 2001), also long term antibiotic therapy (Chowta *et al.,* 2007). *C. parapsilosis* has been particularly implicated to cause intravascular catheter related infections in neonates and pediatric age group (Karlowicz *et al.,* 2000).

The average central venous catheter related blood stream infections rate was 9.26 per 1000 catheter days ranging from 8.64 per 1000 catheter days in PICU to maximum rate of 27.02 per 1000 catheter days in NICU (Chopdekar *et al.,* 2011).

Candiduria has been found to be a risk factor for candidemia and can be indicator of impending sepsis with Candida species in patients admitted to hospitals, especially those in ICUs (Singh *et al.,* 2011; Chander *et al.,* 2013).

In India, a study by Singh *et al.,* reported that the most common risk factor was presence of urinary catheter (63.2%), mechanical ventilation (63.2%), peritoneal dialysis (63.2%) followed by central line insertion (47.4%), diabetes mellitus (26.3%) and use of corticosteroids (21.1%) of patients with fungal colonization of ICU patients (Singh *et al.,* 2011).

National nosocomial infection surveillance system of the center for disease control and prevention, Atlanta, USA, reports a CRBSI rate of 5.8 per 1000 catheter days (NNIS, 1999).

A study by Kaur *et al.,* patients with *C. albicans* colonization had risk factors of duration of stay > 1 week in ICU (36.8 %) and immunosuppressant (31.6%), and patients with NAC colonization had risk factors of multiple organ system involvement (35.5%), indwelling devices (96.8 %), prolonged antibiotic therapy (77.4 %) duration of stay > 1 week (45.2%), use of immunosuppressant

(38.7 %), and diabetes mellitus (35.5 %) which were significantly higher (Kaur *et al.*, 2016).

A study by Fridkin and Jarvis, frequently identified risk factors for fungaemia in hospitalised patients mainly antimicrobial agents, indwelling catheters (CVCs), ICU stay, Hemodialysis, Neutropenia, Hematological/solid organ malignancy (Fridkin and Jarvis, 1996).

However, there are few studies from different parts of the country which give some idea regarding the epidemiology of antifungal resistance among candidemia isolates (Giri and Kindo, 2012).

In the present study, resistant to amphotericin B was noted in 3 isolates (6.25 %). There are very few reports of amphotericin B resistance in Candida isolates from cases of Candidemia in India (Adhikary and Joshi, 2011). Though only 5.8 % isolates of NAC spp. were resistant to amphotericin B, the high frequency of renal toxicity and several other adverse effects limits its use (Deorukhkar and Saini, 2013; Logu *et al.*, 2005).

C. parapsilosis was identified as the most common fungal species in neonates in earlier reports, which is in contrast to our observation. *C. tropicalis* is virulent and is the second leading cause of Candidemia in adults, but is quite infrequent among neonates. Over all, resistance to fluconazole and amphotericin B was 31.7 % and 13.4 % respectively (Basu *et al.*, 2017). A study by Kaur *et al.*, 60 Candida isolates (58.25 %) showed resistant to fluconazole while 7 (6.7 %) isolates showed resistance to amphotericin B (Kaur *et al.*, 2014).

Candidemia in hospitalized patients especially in ICU patients is emerging as a significant problem worldwide. The change in epidemiology and pattern of antifungal susceptibility of Candida infection has made identification of aetiological agent compulsory along with its antifungal susceptibility. Various risk factors have attributed to this increase in Candidemia in the hospital settings. The increase in resistance to antifungal agents among Candida isolates has resulted in increased mortality and morbidity. Prevention of risk factors in Candidemia patients with early removal of central line, timely fungal culture, Candida speciation and antifungal susceptibility are necessary for appropriate treatment and better outcome.

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