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Antifungal Resistance Pattern in Candida Species: Tackling the Emerging Threat to Human Health

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ABSTRACT

Background: *Candida* is yeast like fungus and a normal commensal flora of human body but may be associated with superficial and deep seated fungal infections. *C.albicans* is the most common causative agent of candidiasis; the frequency of other *Non-Albicans Candida* (NAC) species is increasing.

Material and Methods: Samples were processed and identified by standard microbiological methods candida species were isolated from various clinical. Species level identification and Antifungal susceptibility testing was done by using VITEK 2 compact system. Susceptibility was determined using an AST-YS09card, which tests the MIC of 6 antifungals, i.e., FLU, 5-FC, VRC, AMB, CAS, and MFG.

Result: All total 438 isolates of different *candida species* were identified. Among those isolates, *C.albicans* found the most that is 34%, followed by *C.tropicalis*(23%), *C.haemulonii*(16%), *C.krusei*(10%), *C.glabrata*(7%), *C.auris*(6%), and *C.parapsilosis*(4%) respectively. Gender predominance of Candidiasis infection was seen in males (67%). Antifungal susceptibility profile of candida albicans shows maximum resistance to flucytosine(38%), followed by fluconazole(26%), caspofungin(20%), micafungin(16%), amphotericin B(13%), voriconazole(12%) respectively.

Conclusion: Conclusion: Our study shows an increased incidence of *Non albicans Candida* over *C.albicans* showing a significant resistance against various antifungals. There is definitely a need to have a program to monitor the use of antifungals and preventive control measures taken to hinder the further dissemination of antifungals.

Keywords: *Candida, Fungal Infection, Vitek 2, Antifungal Resistance*

1. INTRODUCTION

Candida species is a normal flora of human body found in gastrointestinal tract, mucous membranes or on skin surface but many times found to be associated with superficial and deep seated fungal infections [1]. The most common causative agent of candidiasis is *Candida albicans* but Now a days the incidence of infections due to other *Non-Albicans Candida* (NAC) species is increasing in comparison to *Candida albicans* [2]. More than 90-95% of invasive disease is caused by *C.albicans*, *C.glabrata*, *C.tropicalis*, *C.krusei*, *C.auris* and *C.parapsilosis* [2,3]. Prevalence of infections with high morbidity and mortality due to Candida has been increased [4, 5] with the gradual increase in the resistance to antifungal agents makes clinical treatment difficult. Increasing use of broad spectrum antibiotics with long duration of hospital stay, cytotoxic chemotherapies, intravascular catheters and invasive surgical procedures are few of the pre- disposing risk factors (7). The most common species isolated among *Non-Albicans Candida* is *C.tropicalis* from various clinical types of candidiasis (6). The emergence of *non albicans Candida* species may be due to inclusion of few species like *C.glabrata* and *C.krusei* which

is found to be intrinsically resistant to Fluconazole. The commonly used drug to treat many forms of Candida infections is azole. *C.tropicalis* has the highest adherence rate to the materials such as urinary and vascular catheters. It is involved in formation of biofilm which provides more resistance against antifungal agents. Resistance to azoles has also been increasingly reported in *C. tropicalis* and *C.albicans* (8). Azole Resistance in *Non-Albicans Candida* species was more in comparion to *C.albicans*. Many new antifungal drugs have been licensed in recent years, their resistance is becoming a major concern during treatment of such patients (9).

Aim

The present study was undertaken to study the antifungal resistance pattern of *Candida* species in a tertiary care setting.

2. MATERIAL AND METHODS

This study was conducted in the Department of Microbiology, Santosh Medical College and Hospital, Ghaziabad. All the samples received in microbiology lab from IPD and OPD, were processed and identified by standard microbiological methods and also by Vitek 2 system. All the clinical specimens excluding urine were inoculated on SDA whereas for urine samples CLED agar media was used and then incubated at 37° C aerobically.

Candida species were isolated and identified depending on the morphological features on culture medium, germ tube formation and with the use of Vitek 2 compact system. The isolated colonies were inoculated on SDA and incubated for 72 hrs at 37° C. Growth patterns at 37°C and 42°C were also documented. Samples were analysed based on colony morphology (12).

VITEK 2 Compact System. *Candida species* were identified with the VITEK 2 compact system (BioMérieux Inc., USA) using YST ID REF21343 (Yeast Identification) test cards. The test procedures were performed according to the manufacturer's instructions.

Antifungal Susceptibility Testing- Antifungal susceptibility testing of candida species was done by using VITEK 2 compact system. Susceptibility of isolates was tested using an AST-YS09 card which determines the MIC of 6 antifungals i.e., FLU(fluconazole), 5-FC(flucytosine), VRC(voriconazole), AMB(amphotericin B),CAS (caspofungin) and MFG(micafungin). Suspension was prepared in normal saline as per manufacturer's instruction.

3. RESULTS

Among all clinical sample processed during the study only 438 isolates were identified as *candida species.* The highest no. of *candida spp.* were isolated from blood (30%) followed by sputum (24%), urine (19%), ET culture (9%), swabs (8%) and pus (7%) respectively (fig.1). Among these *Candida* isolates, *C.albicans* were found the most (34%), followed by *C.tropicalis* (23%), *C.haemulonii* (16%), *C.krusei* (10%), *C.glabrata* (7%), *C.auris* (6%) and *C.parapsilosis* (4%)

(fig. 1).

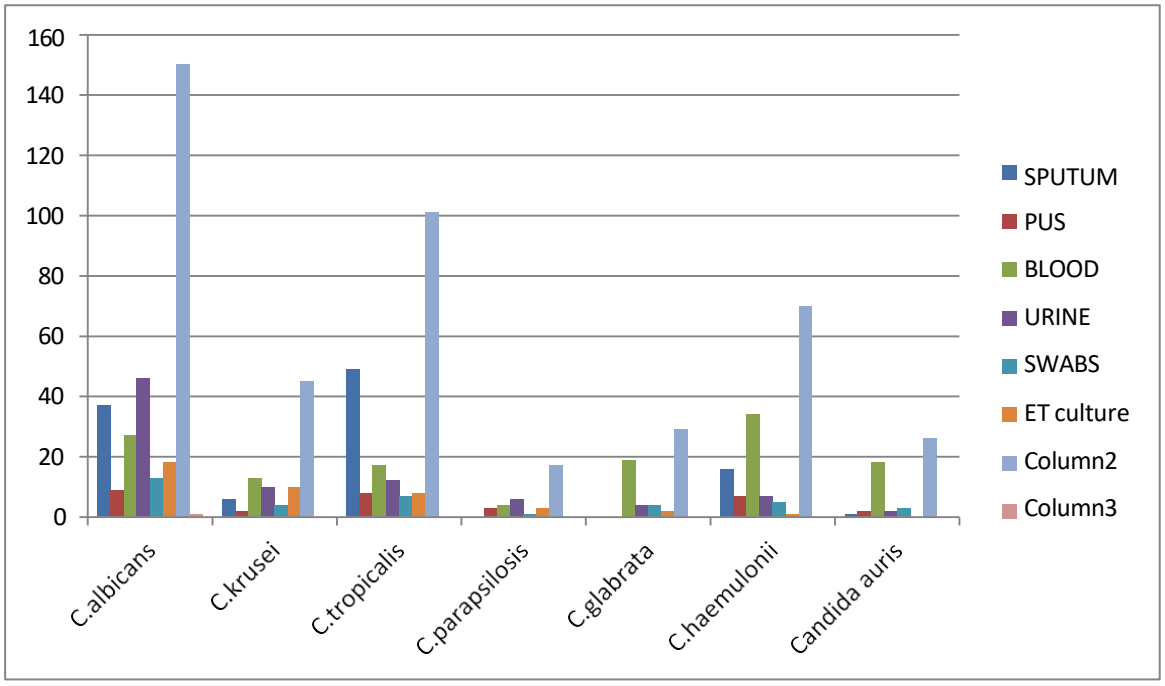

Fig.1 Distribution of Various Candida Species Isolated From Clinical Samples

On the basis of the age of the patients involved, the most no. of candida species were isolated from the age group 41-50 years, followed by age group 31-40 years, then 51-60 years, 61-70 years, 21-30 years, 71-80 years, 81-90 years and least were among age group 11-20 years.

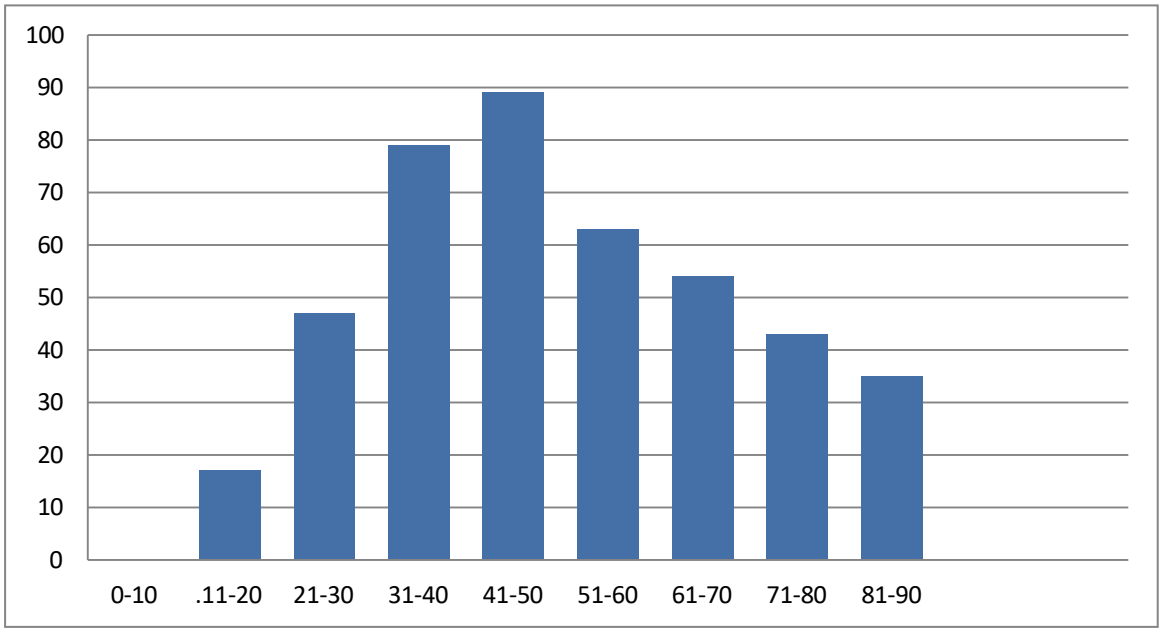

Fig.2 Age wise Distribution of Patients

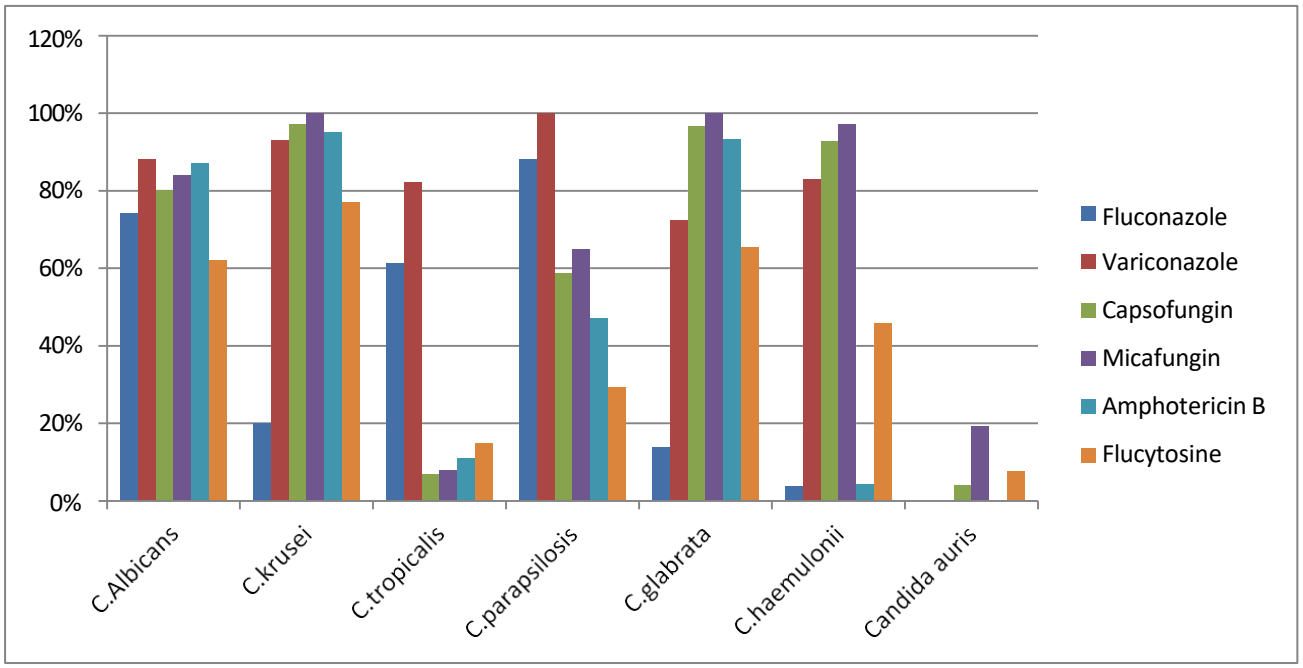

Fig.3 Antifungal Sensitivity Pattern Of Candida Species Isolated

Antifungal susceptibility test was done using Vitek 2. In the present study, antifungal susceptibility profile of *candida albicans* shows maximum resistance to flucytosine, followed by fluconazole, capsofungin, micafungin, amphotericin B, voriconazole respectively. *Candida krusie* shows maximum resistance to fluconazole, followed by flucytosine, but 100% sensitive to micafungin. *Candida tropicalis* shows resistance to caspofungin, followed by micafungin, amphotericin B, Flucytosine, fluconazole, and voriconazole respectively. *C.parapsilosis* shows maximum resistance to flucytosine, amphotericin B, capsofungin, micafungin, fluconazole respectively. *C.glabrata* shows resistance to fluconazole, followed by flucytosine, followed by voriconazole respectively. *C.haemulonii* shows resistance to fluconazole, followed by

amphotericin B, then flucytosine, voriconazole respectively. *C.auris* shows the 100% resistance to amphotericin B, followed by fluconazole, voriconazole, capsofungin, flucytosine and micafungin respectively.

4. DISCUSSION

Incidence of fungal infections have been increasing with an alarming rate over the last two decades. *Candida species* are generally considered as commensals but may act as opportunistic pathogen only due to compromised host defense mechanism. Increase in incidence of fungal infections results in increased morbidity and mortality rate. Our study show that the most fungal infections are the associated with *candida* species and it was found that patients of all age group and both sexes are affected due to candidiasis. In the present study, we have documented predominance of candidiasis infection in males (67%) as seen in other studies (31-33). But another study done by Hatolkar, Swarupa et al females were found to be more commonly affected than males with incidence of 58% and 44% respectively (41). Our study obtained the highest number of *candida* isolates from blood, followed by sputum, urine, ET culture, swabs and pus respectively, which also coincides with the study done by Aijaz N et al in which *candida* was most commonly isolated from blood sample as compared to the other clinical samples.

The significant increased ratio of NAC over *C. albicans* reflected the increased incidence of NAC, but the reason is still not known. The present study also shows the predominance of *Non Albicans Candida* over *Candida Albicans.* Another study by Esmailzadeh et al. (35) and Zakhem et al. (36) reported an increased incidence of NAC compared to *C.albican*. Of the total isolates 56% were NAC while 44% were reported as *Candida albicans* isolates (34). Few more studies have documented higher incidence of *Non-Albicans Candida* ranging from 54-74% (23-25). However, predominance of *C.albicans* was reported in a study done by, Manjunath et al (26, 27). This shift in the frequency from *candida albicans* to NAC such as *C. tropicalis*, *C.glabrata and C. parapsilosi* may be due to the excess use of counter drugs, use of azoles for a longer time and a short term course of antifungal therapy (28). Among the *Non Candida Albicans* in our study *Candida tropicalis* was the predominant one which is also mentioned in a study done by Capoor Malini et al (29) and Naseema Shaik et al (30). Similarly, *C. tropicalis*, was the most common species reported by Jyoti Pal et al (40).

Fungi can cause a wide variety of diseases in humans, for example allergic syndromes to superficial infections, disfiguring and life-threatening invasive fungal diseases (13,14). The treatment of these fungal infections has been based on four classes of antifungal drugs: the polyenes, azoles, echinocandins and the pyrimidine analogue 5-flucytosine (15). *Candida spp.* are the normal commensals of skin and mucosa, but in significant number of cases reported as pathogenic organism due to risk factors such as excess use of broad spectrum of antibiotics, implicit malignancy, HIV infection, organ transplant, long hospital stay due to chronic disease, and exposure to invasive procedures (16,17). *Candida spp.* can cause diverse infections, from blood stream infections (BSIs) to disseminated candidiasis. Regardless of the advanced diagnostic system and available treatment of candidiasis, among the causative agents involved in BSI's, *Candida* ranks fourth in the United States and seventh in Europe (18-21). Data insights showed that *C.tropicalis* resembles *C albicans* in determining resistance to azoles and flucytosine drugs. In this study *Candida albicans* shows maximum resistance to flucytosine, followed by fluconazole, capsofungin, micafungin, amphotericin B, voriconazole respectively. Similarly, Chander J. et al. (37) and Kaur et al (39) in their study obtained higher resistance to fluconazole and low resistance to Amphotericin. However in a study done by Nusrat Aijaz et al, *C. albicans* showed highest resistance to fluconazole followed by voriconazole, flucytosine, caspofungin, micafungin and amohotericin B respectively (38). Our study also reported resistance against voriconazole, micafungin, caspofungin and flucytosine which may be due to reduced susceptibility against fluconazole and cross resistance to the other azoles.

5. CONCLUSION

The present study showed the changing incidence and antifungal pattern of various *candida* species. An increased incidence of *candida* infections in the recent years is seen due to many pre disposing factors like diabetes, immunocompromised condition of patient, COPD (chronic obstructive pulmonary disease), long term antibiotic therapy and excess use of antifungals. Better fungal identification techniques need to be incorporated in routine diagnostic set up. Early detection and antifungal resistance pattern should be determined to provide the better treatment options against the infections and thus benefitting the patients as some of the *candida species* shows intrinsic resistance to few antifungal. Since the present study had many limitations so such kind of more and more studies should be conducted in future to determine the changing pattern as well as to improve the health care settings.

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