

Original Research Article

Candida tropicalis: insight into the characteristics and outcome of adult patients admitted in medical and surgical intensive care units

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ABSTRACT

Background: Non albicans species are emerging increasingly as significant ICU pathogens. The increasing incidence of *C. tropicalis* infections is a significant problem because of its ability to develop rapid resistance to fluconazole.

Methods: The study was designed to isolate, evaluate the risk factors and outcome of *C. tropicalis* infection from intensive care units. Identification was done by the biochemical methods. A total of 89 patients culture positive for *C. tropicalis* were selected for retrospective analysis over a period of one year. We collected various data about risk factors and outcome from the medical records.

Results: A total of 89 patients culture positive for *Candida tropicalis* were analysed. Majority of these culture isolates were obtained from their blood (59.55%) followed by urine samples (31.46%). The indwelling devices (93.2%) remained a highest risk followed by prolonged administration of antibiotic therapy (92.1%) and admission in ICU for more than a week (88.8%). Overall mortality rate was 31.5%. Mortality was higher in patients with longer total length of stay in hospital (89.3%; p 1.000), indwelling devices (85.7%; p 0.5663) and in whom the antimicrobial therapy was administered for prolonged duration (82.1%; p 0.7581), although these factors remained statistically insignificant. 92.1% of isolates were sensitive to amphotericin B and showed 52.8%; 9.0% sensitivity to itraconazole and fluconazole respectively.

Conclusions: *C. tropicalis* is now classified as the third or fourth NAC species being commonly isolated from clinical samples and associated with persistent systemic infections leading to a longer stay in the hospital. Several virulence factors seem to be responsible for high dissemination and mortality.

Keywords: Candidemia, *C. tropicalis*, ICU, Risk factors

INTRODUCTION

The presence of infection in critically ill patients poses unique challenges as it can directly influence the morbidity and mortality. Of the various infections prevalent in an intensive care unit, invasive fungal infection has always been considered to occur infrequently, but, over the past few years, with the surge in broad-spectrum antibiotic usage and improved

knowledge of fungal diseases, the incidence has risen. At present, systemic fungal infections constitute a major problem in intensive care units in both developed and developing nations. However, intensivists in tropical developing countries like India face an uphill task during management of this ever increasing menace of fungal infections.¹ Over the last three decades, *Candida* species has emerged as an important cause of health care associated and opportunistic infections. Although most

infections are attributed to *C. albicans*, the shift towards treatment resistant non-*albicans Candida* (NAC) species is evident in recent years. *C. tropicalis* is one of the most common NAC spp. Isolated from various clinical types of candidiasis. In India, *C. tropicalis* is the most common cause of health care associated candidemia. The increased isolation of *C. tropicalis* from various clinical types of candidiasis is of concern because of its ability to develop rapid resistance to fluconazole.² In *Candida* spp., the transition from commensal to potential pathogen is determined by various host predisposing factors and virulence attributes of infecting species.³ Identifying these virulence factors in infecting pathogens and understanding their effects on the human host are a major challenge for clinical microbiologists. Adhesion of *Candida* spp. to the host epithelial cells is a critical first step in the pathogenesis of infection. Binding of the *Candida* to host cells, host cell proteins, or microbial competitors prevents or at least reduces the extent of clearance by the host's defense mechanisms.⁴

In *Candida*, extracellular hydrolases play an important role in adherence, tissue penetration, invasion, and the destruction of host tissue. Therefore, production of hydrolytic enzymes is one of the important attributes contributing to pathogenesis of *Candida*. Of various hydrolytic enzymes produced by *Candida* spp., phospholipases and proteinases are the most important. Phospholipases damage the host cell membrane and hence facilitate invasion of tissue.³ Although *Candida* is capable of producing exoenzymes, the quantity and potency of these enzymes are different. Production of extracellular hydrolases varies among the species and also depends on the source or site of infection.⁵

The diagnosis of fungal infections in critically ill patients is an extremely difficult task as the symptoms are invariably masked by the presence of dominant primary pathology.¹ Isolation and rapid identification of the infecting pathogen to species level is essential to optimize the early antifungal therapy. But speciation and susceptibility testing of *Candida* is still not being practiced in routine at most of the centers and laboratories and surveillance data regarding the usage of antifungal agents at various hospitals in India is lacking. The main objective was to perform a study on the epidemiology of *Candida tropicalis* infections and evaluation of associated risk factors, antifungal susceptibility profile along with mortality rate resulting from this pathogen isolated from the intensive care units patients at our tertiary care institute.

Aims of study was to get an insight into the present scenario of *Candida tropicalis* infection in patients undergoing treatment in medical and surgical intensive care units and study the antifungal susceptibility pattern that shall facilitate the beginning of empirical antifungal therapy among these patients. Also, to describe the change in epidemiology of *Candida* species and study the

characteristics as well as the outcome of *C. tropicalis* infection among the adult patients.

METHODS

The present study was conducted from January 2015 to December 2015 at the Department of Microbiology, BPS Govt. Medical College for Women, Khanpur Kalan, Sonapat, India, which is a 500 bedded tertiary care hospital. A total of 89 patients admitted in medical and surgical intensive care units that remained culture positive for *C. tropicalis* were included in the study group. Among these patients *C. tropicalis* was isolated from various clinical samples including blood, urine, endotracheal tube and sputum samples. As per the standard operating procedures, all the clinical specimens were inoculated on blood agar and MacConkey agar except blood samples which were inoculated in biphasic brain heart infusion agar plus broth. The culture plates were incubated aerobically at 37°C for 24-48hrs. Colonies appearing pasty, opaque, slightly domed or flat, smooth and pale colored (white, off-white, or beige) with a sweet smell reminiscent of ripe apples were suspected to be colonies of *Candida*.⁶ *C. tropicalis* was identified by HiCandida identification kit and colony color on HiChrome *Candida* agar (HiMedia Laboratories Pvt. Ltd., Mumbai, India). The colony color and morphology on the chromogenic media were interpreted by separate individuals to remove the observer bias for completion of the study in a blinded manner.

No informed consent was obtained because of retrospective nature of the study. The clinical charts of these patients were reviewed retrospectively with the permission of Head of department of medical records to access the patient's documents. Patient's information collected from the medical records included date of admission, age and gender, area of admission: medical/surgical ICU, duration of stay in ICU, total duration of stay in the hospital, underlying medical conditions, associated risk factors such as presence of indwelling devices (central venous catheters, urinary catheter, nasogastric tube, endotracheal tube, respiratory ventilation support etc.), duration of antibiotic therapy, antifungal prophylaxis, exposure to invasive medical procedures, surgical intervention, requirement of vasopressor support, use of corticosteroids, total parenteral nutrition and outcome. Death was defined as death before hospital discharge for primary outcome analysis.

The antifungal susceptibility testing of *C. tropicalis* isolates was performed using Hi-comb minimum inhibitory concentration (MIC) test (Hi-Media Laboratories Pvt. Ltd., Mumbai, India). The antifungal agents tested were Amphotericin B (range 0.002-32µg); fluconazole (range 0.016-256µg) and Itraconazole (range 0.002-32µg). The results of antifungal susceptibility test were interpreted as sensitive (S), susceptible dose-dependent susceptible (SDD), and resistant (R). The

interpretative criteria for azoles were those recommended by the Clinical Laboratory Standard Institute (CLSI).^{7,8} For Amphotericin B, isolates with MICs of $\geq 1\mu\text{g}/\text{mL}$ were categorized as resistant as per Clinical and Laboratory Standards Institute (CLSI 2008) M27-A3 document.⁹

Statistical analysis

Descriptive statistics was used which involves the use of simple percentage and bar chart to analyze the data. In addition, Fisher exact test SPSS v 20 programme (SPSS Inc., Chicago, IL, USA) was performed for comparing the difference between two groups. P value was calculated to determine whether the results obtained were statistically significant. P value of <0.05 was considered as statistically significant

RESULTS

A total of 89 patients culture positive for *Candida tropicalis* were analysed. Majority of these culture isolates were obtained from their blood (59.55%) followed by urine samples (31.46%), endotracheal tube samples (5.62%) and sputum (3.37%) as shown in Table 1.

Table 1: Specimen wise distribution of *Candida tropicalis*.

Specimen	Number (n=89)	Percentage (%)
Blood	53	59.55
Urine	28	31.46
Sputum	3	3.37
Endotracheal tube	5	5.62
Total	89	100

Table 2: Analysis of associated risk factors found for *Candida tropicalis* in ICU patients (n=89).

Characteristics of infected patient	No. Of patients (n=89)	Percentage (%)
Total length of stay in ICU	79	88.8
≥ 1 week	10	11.2
Hospital stay ≥ 10 days	82	92.2
Previous azole agents	54	60.7
Surgical intervention	49	55.1
Diabetes mellitus	48	54
Corticosteroids	22	24.7
Prolonged antibiotic therapy	82	92.1
indwelling devices	83	93.2
Neutropenia	24	27
Haematological disease	08	9
HIV	02	2.2

The risk of developing *C. tropicalis* infection was high in patients who were admitted in ICU for more than a week (88.8%) and even higher in those that remained in the hospital for more than 10 days (92.2%). The indwelling devices (I/V cannulation, foley’s catheter, nasogastric tube, central venous catheter, nasogastric tube and endotracheal tube) remained a high risk factor in 93.2% patients followed by prolonged administration of antibiotic therapy (92.1%). Other associated risk factors in study group are shown in Table 2.

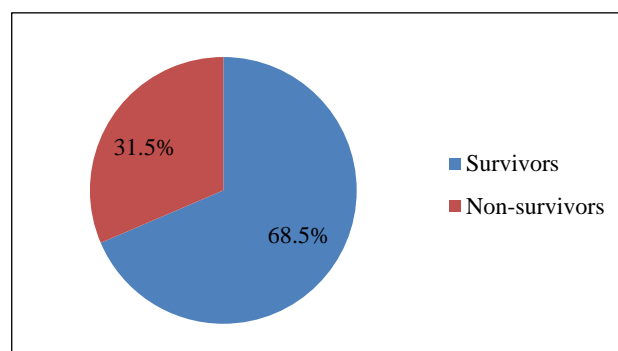


Figure 1: Mortality rate associated with patients infected with *Candida tropicalis*.

Patients infected with *C. tropicalis* exhibited overall mortality rate of 31.5% as shown in Figure 1 and the remaining 68.5% were those who survived the infection.

Table 3: Comparison between survivors and non survivors among patients infected with *Candida tropicalis*.

Factor	Non-survivors N=28	Survivors N=61	P-value
Indwelling devices	24(85.7%)	48(78.7%)	0.5663 (ns)
prolonged use of antibiotics	23(82.1%)	52(85.2)	0.7581(ns)
surgical intervention	14(50%)	40(65.6%)	0.1715(ns)
Neutropenia	10(35.7%)	14(23%)	0.3033 (ns)
Previous azole agents	16(57.1%)	39(64%)	0.6398 (ns)
Corticosteroids	4(14.3%)	11(18%)	0.7678 (ns)
Total length of stay in ICU ≥ 1 week	22(78.6%)	43(70.5%)	0.6076 (ns)
Hospital stay ≥ 10 days	25(89.3%)	55(90.2%)	1.000 (ns)
Diabetes mellitus	9(32.1%)	41(67.2%)	0.0027 (s)
Haematological disease	2(7.1%)	6(9.8%)	1.000 (ns)
HIV	00	2(3.3%)	1.000 (ns)

P value of <0.05 was considered as statistically significant

We revealed that mortality was higher in patients who had longer total length of stay in hospital (89.3%; p 1.000), indwelling devices (85.7%; p 0.5663) and in whom the antimicrobial therapy was administered for

prolonged duration (82.1%; p 0.7581), although these factors remained statistically insignificant (p value >0.05) as shown in Table 3.

Table 4: Antifungal susceptibility pattern of *C. tropicalis* isolated from the study group.

Antifungal drug	Number of isolates	MIC (mg/L)		
		Sensitive	Sensitive Dose Dependent (SDD)	Resistance
Fluconazole	89	8(9.0%)	2(2.2%)	79(88.8%)
Itraconazole	89	47(52.8%)	2(2.2%)	40(44.9%)
Amphotericin B	89	82(92.1%)	-	7(7.9%)

The MICs for the antifungal agents tested are presented in Table 4. Amphotericin B exhibited high efficacy. Out of 89 isolates 92.1% were sensitive and only 7.9% remained resistant to amphotericin B. However, the sensitivity (9.0%) was low to fluconazole whereas moderate (52.8%) to Itraconazole.

DISCUSSION

Patients in ICU are at a higher risk of acquiring nosocomial infections compared with patients in general wards due to the severity of the underlying illnesses and iatrogenic factors related to the high frequency of invasive procedures needed for the monitoring and treatment which include insertion of intravascular catheters, endotracheal intubation, and positive pressure ventilation, urinary catheterization and surgical operations.^{10,11}

In India, *C. tropicalis* is the most common cause of health care associated candidemia.¹² The increased isolation of *C. tropicalis* from various clinical types of candidiasis is of concern because of its ability to develop rapid resistance to fluconazole.¹³ In current study, *C. tropicalis* was most often isolated from blood (59.55%) followed by urine (31.46%), endotracheal tube (5.62%) and sputum (3.37%) as shown in Table 1. In this study, a higher incidence of candidemia was observed in ICU settings. The findings remained in contrast to Kumar S et al who isolated *C. tropicalis* predominantly from urine (51.51%) followed by blood (12.12%), endotracheal aspirate (12.12%), sputum (9.09%) and bronchial aspirate (9.09%).¹⁴

CS Amar et al, also isolated *C. tropicalis* mainly from urine specimens (50%), sputum samples (28.6%) and none from blood samples.¹⁵ Prasobh KK and Udhaya V reported 3.8% of *C. tropicalis* in AFB positive sputum smears.¹⁶

We identified several health care related factors associated with ICU candidemia related to *C. tropicalis*, including presence of indwelling devices (93.2%),

prolonged hospital stay for more than 10 days (92.2%) and prolonged administration of antibiotic therapy (92.1%), suggesting that candidemia might be preventable by lesser usage of unnecessary medical procedures and indwelling devices whenever feasible in ICU settings. Similar results have been reported by Li C who commented that CVC removal rate in their study was only 48.3%, indicating that the awareness of the risk of CVC retention needs to be strengthened in the management of candidemia in ICU patients.¹⁷

In our study previous usage of azole agents was analyzed to be contributing 60.7% as a risk factor for *C. tropicalis* infection in ICU followed by surgical intervention (55.1%) and diabetes mellitus (54%). Clancy CJ et al, showed that the MICs of *Candida* isolates to fluconazole correlated with daily and cumulative doses of fluconazole in the patients with breakthrough infections, and the patients with a higher cumulative dose of fluconazole were more likely to be infected with isolates of *Candida* with higher MICs to fluconazole.¹⁸ Liao X et al, have documented diabetes mellitus among clinical characteristics of patients admitted in ICU as 22%, among which 17.1% in fluconazole sensitive group and 28.9% in fluconazole resistant group.¹⁹

In current study 28 (31.5%) patients died within thirty days of hospitalization. The risk factors and clinical characteristics were compared among non survivors and survivors infected with *C. tropicalis* as shown in Table 3. We found that among non survivors the hospital stay was prolonged for more than 10 days (89.3%; p= 1.000) with total length of stay in ICU more than a week (78.6%; p=0.60). In addition, those who died had a markedly higher retention of indwelling devices (85.7%; p=0.56) with prolonged antibiotic therapy (82.1%; p=0.75), prior intake of azole agents (57.1%; p=0.63) and those who underwent surgical intervention (50%; p=0.17). But all these risk factors or parameters remained statistically insignificant with p value greater than 0.05. Wu Z et al, commented after the multivariate analysis of risk factors associated with mortality of patients with candidemia that central venous catheterization, intravenous nutrition and urinary catheterization remained 100% as risk factors

followed by surgical intervention (98%) in those who died in these episodes and secondly among non survivors 33 (67.3%) patients were identified to be infected with non albicans species.²⁰

The assessment of antifungal drug sensitivity was done for three drugs namely fluconazole, itraconazole and amphotericin B. Out of the 89 *C. tropicalis* isolates, 92.1% isolates remained sensitive to Amphotericin B but exhibited high resistance to fluconazole (88.8% and intermediate resistance to itraconazole (44.9%) as shown in Table 4. Vijaya D et al, reported 100% sensitivity to amphotericin B, with very low (8%) resistance to fluconazole and 36% resistance for itraconazole whereas Jayalakshmi L et al, reported 100% susceptibility to amphotericin B, with 64% and 32.1% resistance to fluconazole and itraconazole respectively.^{21,22} The extensive use of antifungal agents as prolonged therapeutic courses might have led to change in relative prevalence of various *Candida* species with varying antifungal susceptibility patterns in various geographic regions.

CONCLUSION

The current study highlights the preponderance of *C. tropicalis* colonization in ICU patients. For better management of *Non albicans Candida* infection, it shall remain crucial to obtain sufficient epidemiological data of all the species which remain important pathogens among patients admitted in intensive care units. Both infection frequency as well as species distribution must be regularly monitored through well planned advanced studies. The major risk factors were presence of indwelling devices, longer stay in hospital and prolonged usage of antibiotic therapy. This study provides useful descriptive information that shall be useful as a basis for comparison for future studies regarding the prevalence and antifungal susceptibility of *Candida tropicalis* infection at local and international level, which shall pave way for better management of the seriously ill patients under treatment in intensive care units.

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Ethical approval: Not required

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