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Original Article

Candidemia in Pediatric Patients: Changing Pattern of Isolated Candida Species and Risk Factors in Eastern India.

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Abstract

Background: Candidemia is a life-threatening bloodstream infection caused by Candida species and is a major concern in pediatric patients, particularly in developing countries like India. Therefore, the goals of the current study are to isolate and identify several Candida species from blood samples, link various risk factors with candidemia, and ascertain the antifungal sensitivity pattern of each species.

Methodology: This study is an observational, cross-sectional study conducted to determine the prevalence, distribution, and antifungal susceptibility of Candida species among pediatric patients with candidemia. The current study collected blood samples in BACT/ALERT 3D Pediatric bottles for fungal blood culture. After positive growth was obtained from Blood agar and Sabouraud's dextrose agar (SDA), a range of biochemical reactions, including Gram staining, Germ tube test, CHROM agar Candida Medium, and Sugar fermentation, were carried out. The Kirby-Bauer disc diffusion method was used for conducting the antifungal susceptibility test.

Results: Among the total of 156 different species of Candida, the maximum isolates were *Candida albicans* (CA) (42.9%), followed by *Candida tropicalis* (23.1%) and *Candida parapsilosis* (14.7%). The Pediatric Intensive Care Unit (PICU) had the most Candida isolates, and catheterization was a leading risk factor. Susceptibility to Amphotericin B, Caspofungin, and Voriconazole was 84.6%, 81.4%, and 76.9%, respectively. Our study observed that the azole group of antifungals revealed pretty high resistance to Non-Candida albicans (NCA).

Conclusion: The prevalence of candidemia was higher in the pediatric ICU and neonatal ICU, and the incidence rate was highest among neonates and infants. The study concludes that NCA species are gradually replacing *C. albicans* as an important pathogen, and clinicians need to be aware of the antifungal resistance patterns of the different Candida species.

Keywords

Candida Bloodstream Infection, N-Acetyl Cysteine, Azole Group Resistance, *Candida Albicans*.

Introduction

Candida bloodstream infection (BSI) is a significant health burden that causes sepsis and sepsis-related mortality[1]. It is alarming that the mortality rate has increased from 29% to 76%[2,3]. Newborns and young children admitted to the intensive care unit (ICU) are at greater risk of having candidemia[4]. Candida BSI is more likely to occur in newborns weighing less than 2.5 kg, premature infants, central venous catheterization, parenteral nutrition, use of broad-spectrum antibiotics, H2 blockers, immunosuppressive medications, corticosteroids, endotracheal intubation, and prolonged hospital stays[1,5].

Despite its declining percentage, CA is still the most prevalent pathogen among all species of Candida. Recent investigations have found a trend away from Candida albicans species, frequently linked to high mortality and inadequate antifungal susceptibility[6,7]. According to data from the Centers for Disease Control and Prevention and the National Healthcare Safety Network (CDC), Candida species are listed fourth among BSI pathogens and fifth among hospital-acquired pathogens, respectively[8,9,10]. The SENTRY Antimicrobial Surveillance Program has shown that 1,354 Candida species-related infections were found between 2008 and 2009, with 36.5% of them being acquired in the community[11]. It was also found that the prevalence of community-acquired candidemia was much more significant in North America (63.5%) than in Europe (22.4%)[11]. The increasing rate of antifungal resistance among Candida is a substantial cause of mortality and morbidity among neonates and children.

A study by Warris et al.[12] conducted in 23 hospitals in 10 European countries reported 1395 episodes of Candida BSI. They reported a prevalence rate of candidemia of 36.4% among neonates, 13.8% among infants, and 49.8% among children and adolescents. Their study found that the highest prevalence of candidemia was caused by CA (52.5%), followed by *C. parapsilosis* (28%). The highest incidence of candidemia occurred with CA among neonatal patients (60.2%), with the highest rates of *C. parapsilosis* reported in infants (42%). They observed that the incidence of candidemia due to CA was more common than NCA in Northern Europe. Their study also revealed that the mortality rate was higher among patients admitted to the ICU than in other wards.

The goals and outcomes of the current study are to isolate and identify several Candida species from blood samples, link various risk factors with candidemia, and ascertain the antifungal sensitivity pattern of each species. The current study collected blood samples in BACT/ALERT 3D Pediatric bottles for fungal blood culture. After positive growth was obtained from Blood agar and Sabouraud's dextrose agar (SDA), a range of biochemical reactions, including Gram staining, Germ tube test, CHROM agar Candida Medium, and Sugar fermentation, were carried out. The Kirby-Bauer disc diffusion method was used for conducting the antifungal susceptibility test.

Methodology

Study Design

This study is an observational, cross-sectional study conducted to determine the prevalence, distribution, and antifungal susceptibility of Candida species among pediatric patients with candidemia. This hospital-based study was conducted for three years, from June 2019 to June 2022.

Study Site

The study was conducted at the Mycology laboratory in the Department of Microbiology at Burdwan Medical College and Hospital.

Ethics Approval

The Institutional Ethics Committee provided approval for the study.

Sample Size and Selection

A total of 1721 blood samples were collected from patients admitted to the Sick neonatal care unit (SNCU), Pediatric Intensive care unit (PICU), Neonatal ICU (NICU), and pediatric ward. Patients with clinically suspected Sepsis who had a history of prolonged antibiotic therapy and had a central line, intravenous line, endotracheal tube (ET), urinary catheter, or mechanical ventilation were included in the study. Patients without features of Sepsis and those unwilling to provide samples were excluded from the study. Among the 1164 culture-positive blood samples, 156 were revealed to have positive growth for Candida.

Inclusion & Exclusion criteria

Patients with clinically suspected Sepsis (patient admitted in PICU, NICU, PW with more than 48 hrs stay) with a history of prolonged antibiotic therapy and having a central line, intravenous line, ET, urinary catheter were included in the study. Patients without features of Sepsis and patients/guardians of patients who were unwilling to give the samples were excluded from the study.

Data Collection

Data on patient demographics, clinical characteristics, risk factors for candidemia, and laboratory results were collected using a standardized data collection form. Blood samples were collected aseptically and cultured using standard laboratory protocols for fungal growth. Candida isolates were identified at the species level using biochemical tests. MALDI-TOF MS. Antifungal susceptibility testing (AFST) was performed using the broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

Growth detection and species identification

BACT/ALERT system gave the signal for microbial growth. Blood samples were drawn from culture positive BACT/ALERT bottles, inoculated on blood agar and Sabouraud's dextrose agar (SDA), and incubated at 37ºC for 24-48 hours. After 24-48 hours, growth was obtained from SDA and blood agar media (Figure 1). An array of biochemical tests was carried out. Gram stain was done to identify the morphology of budding yeast cells. The germ tube test was done to differentiate between CA and NCA. We performed Chlamydospore to identify the different species of Candida. Presumptive identification of various species of Candida was made using CHROM agar Candida Medium.

KB006 HiCandida Identification Kit was used for sugar fermentation and biochemical tests (Table 1 & Figure 2). Antifungal Susceptibility Test (AFST) was performed using Amphotericin-B (20 mcg/disc), Voriconazole (1 mcg/disc), Caspofungin (5 mcg/disc), Itraconazole (10 mcg/disc), and Fluconazole (25 mcg/disc) in the disc diffusion technique of AFST. All these discs were commercially prepared and ordered from Hi-Media (India). AFST media was prepared by adding 2% glucose and methylene blue dye 5 microgram/ml in Mueller Hinton agar[9]. The zone of inhibition around the disc was calculated after 48 hours of incubation (Figure 3)[13,14].

Table 1: Interpretation of Sugar fermentation Tests of CA and NCA by using KB006 HiCandida Identification Kit.

Candida spp	Urease	Melibiose	Lactose	Maltose	Sucrose	Galactose	Cellpbiose	Inositol	Xylose	Dulcitol	Raffinose	Trehalose
C. albicans	N	N	N	N	N	P	P	N	N	P	N	P
C. glabrata	P	N	N	N	N	N	N	N	N	N	N	N
C. tropicalis	N	N	N	N	N	N	P	N	N	N	N	N
C. parapsilosis	N	N	N	P	P	P	P	N	N	P	P	P
C. krusei	P	N	N	N	N	N	N	N	N	N	N	N

NCA-Non-Candida albicans; CA-Candida albicans; N=Negative; P=Positive.

Data Analysis

Descriptive statistics were used to summarize the data. The prevalence of Candida species was calculated as the percentage of positive cultures out of the total number of blood samples tested. The distribution of Candida species was reported as the percentage of each species out of the total number of Candida isolates. The prevalence and distribution of Candida species were also stratified by ICU and ward and by patient age group. The percentage of patients with risk factors for candidemia was reported.

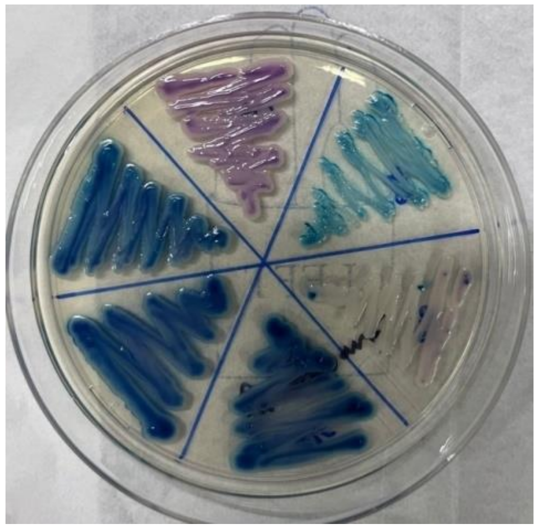

Figure 1: Chrome agar Candida medium.

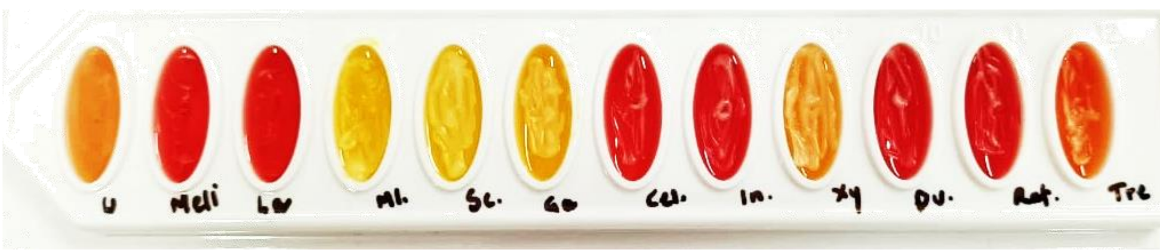

Figure 2: The interpretation of sugar fermentation and biochemical Test kits (KB006 HiCandida Identification Kit).

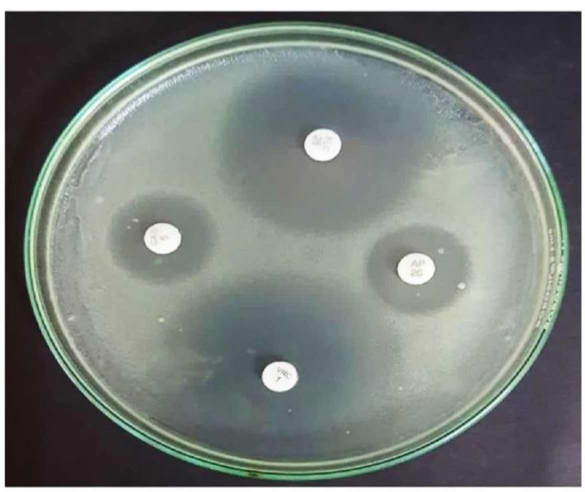

Figure 3: Antifungal susceptibility test (AFST).

Results

Of the 1721 blood samples, 1164 (67.6%) were culture-positive for Candida species. Of these, 156 (13.4%) were CA, and 1008 (86.6%) were NCA species. Among the NCA isolates, *C. tropicalis* (23.1%) was the most prevalent, followed by *C. parapsilosis* (14.7%), *C. krusei* (12.2%), and *C. glabrata* (7.1%). The most NCA isolates were obtained from the PICU (31 isolates), followed by the NICU (30 isolates). Most candidemia cases were observed in neonates (30.1%) and infants (27%).

The most common risk factors for candidemia were Sepsis or septic shock (65.4%), pneumonia (26.3%), and urinary tract infection (8.3%). A significant proportion of candidemia cases had indwelling medical devices (29.5%), were on a mechanical ventilator (26.3%), had a prolonged hospital stay (22.4%), or were using broad-spectrum antibiotics (21.8%).

The AFST results showed that amphotericin B (84.6%) and caspofungin (81.4%) had the highest efficacy against Candida species, followed by voriconazole (76.9%) and itraconazole (71.8%). Fluconazole showed the lowest efficacy (59.6%). CA was most sensitive to amphotericin B (86.6%) and caspofungin (79.1%), while *C. tropicalis* was most sensitive to caspofungin (88.9%) and voriconazole (77.8%). *C. parapsilosis* showed good efficacy towards caspofungin (87%) and amphotericin B (82.6%). *C. krusei* was most sensitive to amphotericin B and itraconazole (94.7%), while *C. glabrata* showed high efficacy against amphotericin B and itraconazole.

Table 2: Distribution of CA and NCA among the different ICUs and wards.

Wards/ICU	CA n= 67(42.9%)	NCA; (n=89) *C.tropicalis* n=36(23.1%)	*C.parapsilosis* n=23(14.7%)	*C. krusei* n=19(12.2%)	*C.glabrata* n=11(7.1%)	Total (n=156) NCA (n=89)	Total (CA+NCA) n=67+89 =156
PICU	26(38.8)	12(33.3)	9(39.1)	6(31.6)	4(36.4)	31(34.8)	57(36.5)
NICU	17(25.37)	12(33.3)	7(30.4)	8(42.1)	3(27.3)	30(33.7)	47(30.1)
SNCU	14(20.9)	8(22.2)	5(21.7)	2(10.5)	2(18.2)	17(19.1)	31(19.9)
Pediatric ward	10(14.9)	4(11.1)	2(8.7)	3(15.8)	2(18.2)	11(12.4)	21(13.5)

NCA-Non-Candida albicans; CA-Candida albicans; PICU-Pediatric intensive care unit; NICU-Neonatal intensive care unit; SNCU-Special Newborn Care Unit.

Table 3: Diagnosis and age-wise distribution of different species of *Candida*.

Age group	Sepsis/Septic shock n=102(65.4%) CA (n= 42)	Sepsis/Septic shock NCA (n=60)	Pneumonia n=41(26.3%) CA (n=20)	Pneumonia NCA (n=21)	UTI n=13(8.33%) CA (n=5)	UTI NCA (n=8)	Total (n=156) CA (n=67)	Total NCA (n=89)	Total (CA+NCA) n=156
Neonates (≤28 days)	11(26.2)	21(35)	5(25)	6(28.6)	1(20)	3(37.5)	17(25.4)	30(33.7)	47(30.1)
Infants (>28 days to 1 year)	9(21.4)	14(23.3)	8(40)	6(28.6)	3(60)	2(25)	20(29.9)	22(24.7)	42(27)
>1 to 2 years	10(23.8)	12(20)	4(20)	6(28.6)	1(20)	3(37.5)	15(22.4)	21(23.6)	36(23.1)
>2 to 5 years	7(16.7)	5(8.3)	2(10)	2(9.5)	_	_	9(13.4)	7(7.9)	16(10.3)
>5 years	5(12)	8(13.3)	1(5)	1(4.8)	_	_	6(9)	9(10.10)	15(9.5)

Table 4: Risk factors wise distribution of different species of Candida.

Risk factors	CA (n=67)	NCA (n=89)					Total (n=156)
		C. tropicalis (n=36)	*C. parapsilosis* (n=23)	*C. krusei* (n=19)	*C. glabrata* (n=11)	NCA (n =89)	Total (CA+NCA) (n=156)
Mechanical ventilation	17(25.4)	12(33.3)	5(21.7)	6(31.6)	1(9)	24(27)	41(26.3)
Catheter in–situ	20(29.9)	11(30.6)	6(26.1)	5(26.3)	4(36.4)	26(29.2)	46(29.5)
Usages of antibiotics with a broad spectrum	14(20.9)	8(22.2)	6(26.1)	4(21)	2(18.2)	20(22.5)	34(21.8)
Prolonged stay in hospital <14 days	16(23.9)	5(13.9)	6(26.1)	4(21)	4(36.4)	19(21.3)	35(22.4)

Table 5: The distribution of antifungal susceptibility pattern of CA and NCA.

Species of candida	Amphotericin B		Fluconazole		Voriconazole		Caspofungin		Itraconazole	
	S	R	S	R	S	R	S	R	S	R
CA (n= 67)	58(86.6)	9(13.4)	32(47.8)	35(52.2)	51(76.1)	(23.9)	53(79.1)	14(20.9)	46(68.7)	21(31.3)
***C. tropicalis* (n=36)**	27(75)	9(25)	17(47.2)	19(52.8)	28(77.8)	8(22.2)	32(88.9)	4(11.1)	24(66.7)	12(33.3)
***C. parapsilosis* (n=23)**	19(82.6)	4(17.4)	18(78.3)	5(21.7)	17(73.9)	6(26.1)	20(87)	3(13)	15(65.2)	8(34.8)
***C. krusei* (n=19)**	18(94.7)	1(5.3)	17(89.5)	2(10.5)	16(84.2)	3(15.8)	16(84.2)	3(15.8)	18(94.7)	1(5.3)
***C. glabrata* (n=11)**	10(90.9)	1(9.1)	9(81.8)	2(18.2)	8(72.7)	3(27.3)	6(54.5)	5(45.5)	9(81.81)	2(18.2)
Total (CA+NCA) n=156	132(84.6)	24(15.4)	93(59.6)	63(40.4)	120(76.9)	36(23.1)	127(81.4)	29(18.6)	112(71.8)	44(28.2)

NCA-Non-Candida albicans; CA-Candida albicans; S-Sensitivity; R-Resistance.

Discussion

The newly discovered and potentially fatal condition known as Candida BSI poses a risk to patients hospitalized in different wards and ICUs. In the current study, candidemia was identified among 9.1% of all patients with a Sepsis history. The most typical isolation of the Candida genus was CA, next to it was Candida tropicalis and *C. parapsilosis.* An epidemiological shift to NCA from CA was observed in this study. However, this finding was similar to a study, where they revealed 64 % NCA compared to 36% CA[15]. Contrary to findings from previously published research, this trend was also noted in a few studies[16,17]. Throughout the last several decades, the epidemiology of candidemia has changed as NCA, particularly *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*, have gradually replaced CA as the pivotal pathogen. The burgeoning importance of NAC (N-Acetyl Cysteine) and the disease burden caused by them is a major concern for clinicians[17,18]. Khadka et al. have reported similar findings in relation to our study, where they have revealed that the major isolates of their study are *C. tropicalis* among NCA followed by *C. glabrata*[18]. Furthermore, our findings show that NCA species have been gradually displacing Candida albicans as an important pathogen over the past two to three decades, as shown by several comparable earlier investigations to our own. Candida that is not CA directly influences the choice of traditional antifungal therapy[19]. The pediatric population is a very vulnerable age group suffering from Candida BSI. The PICU had the maximum prevalence rate of candidemia in the current research (36.7%), followed by the NICU (30.1%). Corresponding to this, several researchers found that ICUs had higher prevalence rates of candidemia than wards[2]. Similar to our study, another study revealed that CA and NCAs BSIs had 43.5% and 56.5% incidence rates, respectively, in the newborn ICU of Child Healthcare[20].

In this current study, we have reported a 30.1% prevalence rate of candidemia among neonates, followed by among infants (27%). We have observed that as age increases, the prevalence of infection decreases. So, we have concluded that the prevalence of candidemia is inversely proportionate to aging. This scenario was quite similar in other studies where the authors found a high prevalence rate of candidemia among neonates (35%)[2,21]. It is attributed that at a young age, the immune system is so naïve that the neonates and young children fail to build up immunity in their bodies. As a result, Candida takes the upper hand and invades the bloodstream, causing bloodstream infection. We observed that 65.4% of the isolates were obtained from patients suffering from Sepsis or septic shock, 26.3 % suffering from pneumonia, and 8.3% were diagnosed with Urinary tract infection (UTI). Similarly, another study revealed a high incidence of candidemia among those patients who were suffering from septic shock[22].

The important factor associated with candidemia is the colonization of Candida on the skin and the mucosal membrane. Candida can potentially break the bridge between our skin and the mucus membrane. The intravascular catheters or mechanical ventilators or surgery, or burns are the pivotal factors that accelerate the disruption of our epithelial barrier in patients suffering Candida BSI[18]. In the current investigation, we found that patients who were on a mechanical ventilator (26.3%) or a catheter (29.5%) had a greater prevalence of candidemia. Similar to this, a prior study found that patients on central lines and receiving mechanical ventilation had a significant rate of candidemia[22]. However, a study by Khairat et al. reported that long-term use of antibiotics is the leading risk factor associated with candidemia, followed by the presence of central line[2].

Because of this, the right antifungal drug must be able to handle this risk. In recent years, testing for antifungal susceptibility has been standardized and now serves the same purpose as testing for antibacterial susceptibility in microbiology labs. Amphotericin B was found to be sensitive to 84.6% of the isolates. Similarly, the Khairat et al. study found that Amphotericin-B sensitivity occurs often[2]. The increasing resistance pattern of Amphotericin–B is a great concern for the clinician for treating candidemia. The random use of Amphotericin–B, unjudicial use of broad-spectrum antibiotics, long tern presence of catheter-in-situ are the main risk factors for the emergence of Amphotericin–B resistance[2]. Some previous studies in the past decades had reported almost no resistance to Amphotericin-B at all[17,18]. In the current study, caspofungin showed 81.4% sensitivity. Similarly, another study revealed a high sensitivity rate to Caspofungin[2].

Voriconazole, Itraconazole, and Fluconazole revealed 76.9%, 71.8%, and 59.6% sensitivity rates, respectively. Some other studies reported similar findings[2]. A study done by Caggiano revealed pretty much lower resistance rate to Fluconazole and Voriconazole[16]. Some investigations have been conducted into the relationship between in vitro outcomes and patient outcomes. The results revealed that the mortality and morbidity are very high in patients with resistant strains compared to those patients with susceptible Candida isolates. These investigations have made it possible to create interpretive breakpoints for Candida sp, the most prevalent cause of candidemia worldwide[2,22]. In conclusion, antifungal susceptibility tests have evolved into crucial instruments for guiding the treatment of fungal illnesses, understanding local and global disease epidemiology, and detecting antifungal resistance. Hence, it is imperative to identify the Candida up to species level and proper antifungal susceptibility and report them as soon as possible. Every lab should have enough resources to do so. The clinician should be more cautious regarding the selection and duration of broad-section antibiotic use. The early removal of a central line or urine catheter and proper hand hygiene maintenance also play a pivotal role in controlling the disease burden caused by Candida.

Conclusion

This study reports the prevalence of candidemia in hospitalized patients and their susceptibility to antifungal agents. Of the 1721 blood samples, 67.6% were culture-positive for Candida species, with 13.4% being CA and 86.6% NCA species. The most prevalent NCA species were *C. tropicalis, C. parapsilosis, C. krusei,* and *C. glabrata*. The most common risk factors for candidemia were Sepsis or septic shock, pneumonia, and urinary tract infection. The study found that amphotericin B and caspofungin had the highest efficacy against Candida species, while fluconazole had the lowest. The prevalence of candidemia was higher in the pediatric ICU and neonatal ICU, and the incidence rate was highest among neonates and infants. The study concludes that NCA species are gradually replacing CA as an important pathogen, and clinicians need to be aware of the antifungal resistance patterns of the different Candida species.

Conflicts of Interest

The authors declare no conflicts of interests.

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