ORIGINAL ARTICLE

Candidemia in a Pediatric Population: A 10-year Indian Study

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Abstract

Introduction: Candidemia has emerged as one of the life-threatening causes of invasive infection in both adults and children worldwide.

Materials and methods: We performed a retrospective study of children (≤16 years) with candidemia diagnosed in our center in 2010 to 2019. Demographics, comorbidities, *Candida* species distribution, antifungal susceptibility, and outcomes were analyzed.

Results: A total of 96 children were identified in the last 10 years. The predominant species identified were *C. tropicalis* (23%), *C. parapsilosis* (15.6%), *C. pelliculosa* (15.6%), *C. albicans* (13.6%), *C. krusei* (7.3%), and *C. haemulonii* (5.2%). Male to female ratio was 2:1. The most common risk factor was found to be congenital malformations (27%), followed by hematological malignancy in 13.5%. Candidemia was diagnosed while being admitted in the intensive care unit in 74%, 14.5% in wards, and 11.5% in outpatients. The overall mortality rate was found to be 31.3%. *C. tropicalis* was found to be sensitive to fluconazole in 95.5%, flucytocine in 95.2%, and 100% susceptible to amphotericin B, voriconazole, and caspofungin.

Conclusion: Invasive candidiasis occurs frequently in hospitalized patients and is associated with high mortality rates. *C. tropicalis* was the most frequently isolated species. We have observed a shift in *Candida* spp. with an increasing isolation of *C. pelliculosa*. The occurrence of azole resistance is a matter of concern.

Clinical significance: This type of data analysis is needed to track trends of serious infection and to develop guidelines for infection control strategies and antimicrobial stewardship program.

Keywords: Candidemia, Children, Invasive candidiasis.

Pediatric Infectious Disease (2021): 10.5005/jp-journals-10081-1255

Introduction

The yeast belonging to the genus *Candida* forms a part of the normal skin and mucosal flora in humans. It is capable of causing invasive candidiasis which includes, among other clinical manifestations, intra-abdominal infections, osteomyelitis, and bloodstream infections (candidemia). Candidemia being the most common type of invasive candidiasis remains a serious cause of illness with fatal outcome globally.[1] Data from the National Healthcare Safety Network have identified *Candida* species as the fifth most common cause of healthcare infection in hospitalized US patients behind coagulase-negative *Staphylococci*.[2] In a review article, the fungi have been documented as the second most common pathogen isolated in hospitalized septic children and found to be the leading cause of death in cancer children or following transplant, mostly in an organ or hematopoietic stem cell transplant.[3]

There are also reports suggesting an increase in candidemia.[4–6] Advances in medical and surgical management have attributed to an increase in invasive candidiasis. Other associated risk factors include severe trauma, long-term use of antibiotics, major surgical procedures, mucosal colonization by *Candida* spp., indwelling vascular catheters or prosthetic devices, total parenteral nutrition, immunosuppressive therapy, premature infants, and use of mechanical ventilator support.[1,7–10]

Candidemias are reported worldwide in all age-groups, especially among critically ill, immunocompromised patients or those with complicated medical condition.[11] It is often associated with prolonged hospitalizations, high healthcare costs, substantial morbidity, and all-cause in-hospital mortality of up to 30%.[1]

There are more than 17 species of *Candida* causing invasive candidiasis in humans. More than 90% of these infections are due to five species: *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*. The list of reported species will continue to grow with modern methods of identification.[6,12,13]

C. albicans is the most common species causing candidiasis in the United States.[1] However, significant geographical differences in species distribution have been observed.[6,14] A shift in the epidemiology of candidemia from *C. albicans* toward non-*albicans Candida* spp. has been a global concern in recent times.[6,9,10,14,15] There has been an increase in the proportion of infections due to *C. glabrata* and *C. parapsilosis* in the last few decades. These species show higher levels of resistance to antifungal agents and therefore might be associated with higher mortality than *C. albicans*.[1,9] Equally concerning is *C. auris*, a multidrug resistant, emerging agent of candidemia. It was first described in 2009 and has since been reported in 30 countries, including India.[1,16] Understanding the epidemiology of *Candida* species is critical, as clinicians often begin

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How to cite this article: Adhikary R, Venkatesh BM, Joshi S, *et al.* Candidemia in a Pediatric Population: A 10-year Indian Study. Pediatr Inf Dis 2021;3(1):1–8.

Source of support: Nil

Conflict of interest: None

empiric therapy before antifungal susceptibilities are reported from the isolate.

Materials and Methods

A retrospective analysis of all cases of candidemia in children was carried out from January 1, 2010, to December 31, 2019, in a single 600-bed tertiary-care hospital in southern India. Candidemia was defined as an isolation of *Candida* species from one or more blood cultures in a patient with supportive clinical correlation.

All candidemia were identified through the microbiological laboratory database. Data regarding demographic characteristics and clinical risk factors were collected from the hospital information system. All children were categorized into four age-groups: neonate (birth to <1 month), infant (1 month to <2 years), children (2 to <12 years), and adolescent (12–16 years).

Blood samples were collected under aseptic condition in BacT/ALERT (bioMerieux) culture bottles for aerobic bacterial and fungal growth and incubated at 37°C for 7 days. When BactAlert indicated positive, bottles were unloaded and preliminary Gram stain and subcultures were made on 5% sheep blood agar and MacConkey agar. The isolates were further identified into species level by (a) germ tube production, (b) pigmentation on chromogenic medium (CHROM agar Candida), and (c) carbohydrate assimilation tests using the VITEK 2 compact system (bioMerieux). Adequate quality control measures were undertaken with reference strains *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019.

Antifungal susceptibility was also done for fluconazole, amphotericin B, voriconazole, flucytosine, caspofungin, and micafungin in VITEK 2 compact system. The interpretative minimum inhibitory concentration (MIC) breakpoints of the tested antifungals (fluconazole, voriconazole, caspofungin, and micafungin) were those suggested by the CLSI M27-A3 document, and for amphotericin B it was based on EUCAST guidelines.[17,18] For flucytosine, the categorical result was obtained according to the breakpoints provided by the VITEK-2 system.[19]

Results

There were 123 different episodes of candidemia detected in 96 children during the 10-year study period. Eighteen patients had more than one episode of candidemia. One patient had two different *Candida* species in a single episode. Only the first isolate of the patient (total 96 isolates) was taken into consideration for the study. Most of the blood isolates have been caused by non-*C. albicans* (86.4%). Overall, *C. tropicalis* accounted for 23% of the isolates, followed by *C. parapsilosis* and *C. pelliculosa* at 15.6%, *C. albicans at* 13.6%, *C. krusei* at 7.3%, *C. haemulonii* at 5.2%, *C. lipolytica* and *C. famata* at 3.1%, and relatively rare were *C. glabrata*, *C. guilliermondii*, *C. lusitaniae*, and *C. utilis* at 2.1%. Five isolates (5.2%) of *Candida* were not identified to species.

Overall, a total of 55 (57.3%) isolates were seen in 2010 to 2014, and 41 (42.7%) isolates in 2015 to 2019. Three new species, *C. famata*, *C. glabrata*, and *C. utilis* were seen in 2015 to 2019. The increased isolation of *C. pelliculosa* from 5 isolates in 2010 to 2014 to 10 isolates in 2015 to 2019 was found to be statistically significant with a *p* value of 0.04. *C. famata* was also found to be statistically significant with a *p* value of 0.04, as 3 cases were reported in 2015–2019 and nil in 2010–2014. The Chi-square test was used for analysis of trends across years. In 2010 to 2014, *C. tropicalis* was the most common isolate, followed by *C. albicans*, and *C. parapsilosis*. But in 2015 to 2019, *C. pelliculosa* was the most common isolate followed by *C. tropicalis and C. parapsilosis*. Table 1 shows species distribution of 96 *Candida* bloodstream isolates in 2 groups of 5 years, 2010 to 2014 and 2015 to 2019.

We have isolated 74% of the isolates from ICU, 14.5% from inpatients, and 11.5% from outpatients. It is to be noted that *C. pelliculosa* ($n = 15$), *C. lusitaniae* ($n = 2$), and *C. utilis* ($n = 2$) were isolated from patients admitted in the ICU. In contrast, *C. guilliermondii* ($n = 2$) was found in patients admitted in the ward as summarized in Table 2.

We identified 31 (32.3%) neonates, 42 (43.8%) infants, 18 (18.8%) children, and 5 (5.2%) adolescents with *Candida* bloodstream infection (BSI). Therefore, 76% of the isolates were seen from birth up to <2 years. Both *C. tropicalis* (22.6%) and *C. pelliculosa* (22.6%) were the predominant species isolated in neonates; *C. famata*, *C. glabrata,* and *C. utilis* were not found in in this age-group. But in the infants, *C. tropicalis* (23.8%) followed by *C. albicans* (16.7%) were isolated more frequently. Among the children, *C. parapsilosis* (33.3%) followed by *C. tropicalis* (16.7%) and in adolescents; *C. tropicalis* (40%) was most frequently isolated. Table 3 shows distribution of *Candida* species according to age-group.

The demographic study of the 96 candidemia patients showed that the median age was 2 years (range, 7 days to ≤16 years) with 66.7% males and 33.3% females. In relation to clinical characteristics, 27.1% of candidemia occurred in children with congenital malformation, followed by hematological malignancy in 13.5%. Other predisposing factors are lung disease (9.4%), prematurity (8.3%), surgery (7.3%), septic shock (6.3%), neonatal sepsis (6.3%), low birth weight (4.2%); low APGAR score, and other medical condition (3.1%); cardiovascular disease, hemodialysis, renal failure, trauma, IUGR, fever seizure, and respiratory distress each at 2.1%; and diabetes mellitus and solid malignancy each at 1%. The demographic details and clinical characteristics of the patients are summarized in Table 4.

The overall mortality in our study was found to be 31.3 % (30/96). The *Candida* species included were *C. pelliculosa* (7,

Table 1: Species distribution of 96 *Candida* bloodstream isolates in southern India, 2010–2019

	No. (%) of isolates			
Species	*2010–2014*	*2015–2019*	*Total*	*p*[a]
C. tropicalis	14 (25.4)	8 (19.5)	22 (23)	0.49
C. parapsilosis	8 (14.5)	7 (17)	15 (15.6)	0.74
C. pelliculosa	5 (9.1)	10 (24.3)	15 (15.6)	0.04
C. albicans	10 (18.2)	3 (7.3)	13 (13.6)	0.12
C. krusei	5 (9.1)	2 (5)	7 (7.3)	0.43
Candida. species non-albicans	4 (7.3)	1 (2.4)	5 (5.2)	0.29
C. haemulonii	3 (5.4)	2 (5)	5 (5.2)	0.90
C. lipolytica	3 (5.4)	0	3 (3.1)	0.13
C. famata	0	3 (7.3)	3 (3.1)	0.04
C. glabrata	0	2 (5)	2 (2.1)	0.10
C. guilliermondii	1 (1.8)	1 (2.4)	2 (2.1)	0.83
C. lusitaniae	2 (3.6)	0	2 (2.1)	0.22
C. utilis	0	2 (5)	2 (2.1)	0.10
Total	55 (57.3%)	41 (42.7%)	96	

[a]Chi-squared test for trend

23.3%), *C. tropicalis* (6, 20%), *C. parapsilosis* (5, 16.7%), *C. albicans* (3, 10%), *C. haemulonii* (3, 10%), *C. krusei* (3, 10%), *C. famata* (1, 3.3%), *C. guilliermondii* (1, 3.3%), *Candida* spp. non *albicans* (1, 3.3%). All the children with *C. lipolytica* (3), *C. glabrata* (2), *C. lusitaniae* (2), and *C. utilis* (2) recovered from candidemia. Table 5 shows number of died patients in each category of *Candida* spp.

Out of a total number of 71 intensive care unit (ICU) patients, 14 inpatients and 11 outpatients, 24 (33.8%), 4 (28.6%), and 2 (18.2%), respectively, in each group had a fatal outcome. Six patients from ICU were discharged on request and were lost to follow-up. The mortality was found to be 29% among the neonates, 23.8% among the infant, 39% among the children, and 80% among the adolescent age-groups. This was found to be statistically significant in the age group of birth to <2 years when compared 2 to 16 years (p value = 0.04). Location and age-wise distribution of the expired candidemia cases are summarized in Table 6.

Table 2: Species distribution and location of 96 *Candida* species bloodstream infection

Species	*Total no. (%) of isolates 2010–2019*	*ICU total no. (%)*	*IP total no. (%)*	*OP total no. (%)*
C. tropicalis	22 (23)	18 (25.3)	2 (14.3)	2 (18.2)
C. parapsilosis	15 (15.6)	8 (11.3)	3 (21.4)	4 (36.4)
C. pelliculosa	15 (15.6)	15 (22.1)	0	0
C. albicans	13 (13.6)	10 (14)	1 (7.1)	2 (18.2)
C. krusei	7 (7.3)	5 (7)		2 (18.2)
Candida. species non-albicans	5 (5.2)	2 (2.8)	2 (14.3)	1 (9.1)
C. haemulonii	5 (5.2)	4 (5.6)	1 (7.1)	0
C. lipolytica	3 (3.1)	3 (4.2)	0	0
C. famata	3 (3.1)	1 (1.4)	2 (14.3)	0
C. glabrata	2 (2.1)	1 (1.4)	1 (7.1)	0
C. guilliermondii	2 (2.1)	0	2 (14.3)	0
C. lusitaniae	2 (2.1)	2 (2.8)	0	0
C. utilis	2 (2.1)	2 (2.8)	0	0
Total	96	71 (74)	14 (14.5)	11 (11.5)

Among the 96 isolates, 94 isolates were available for the susceptibilities of antifungal agents. For all 94 *Candida* BSI isolates combined, the activity of each agent (μg/mL), expressed as the MIC_{50}/MIC_{90} (and the percentage of susceptible isolates), was as follows: fluconazole, 1/8 (71%); amphotericin B, 0.5/1 (91.5%); voriconazole, ≤0.12/0.25 (99%); flucytosine, ≤1/8 (87.8%); caspofungin, ≤.25/0.5 (94%); and micafungin, 0.5/0.12 (100%). *C. tropicalis*, the most commonly isolated species, was 95.5% sensitive to fluconazole, 95.2% sensitive to flucytosine, and 100% sensitive to amphotericin B, voriconazole, caspofungin, and micafungin. The isolates in which no interpretable breakpoints exist in CLSI/EUCAST, the MIC values and the range of the measured MICs are given, and no statement concerning the clinical sensitivity could be made. All seven *C. krusei* isolates are considered to be resistant to fluconazole, irrespective of their MIC. The *in vitro* antifungal susceptibilities as determined by VITEK 2 system is summarized in Table 7.

Discussion

Significant geographic variation among BSI due to *Candida* spp. is observed in different parts of the world. In our study in pediatric age-group, BSIs due to non-*Candida albicans* spp. were more common (86.4%) than *C. albicans* (13.6%). This finding is consistent with other studies from Turkey, Saudi Arabia, India, and Mexico.[7,10,20–23] An important finding from an Indian study was the emergence of *Candida* spp. as the second most common cause of BSI in pediatric ICUs (PICU) after coagulase-negative *Staphylococcus*, instead of gram-negative bacteria.[20] In our study, the top five isolates were *C. tropicalis* (23%), *C. parapsilosis* (15.6%), *C. pelliculosa* (15.6%), *C. albicans* (13.6), and *C. krusei* (7.3%). In a study from North India, *C. tropicalis* (39%) was the commonest isolate recovered, followed by *C. parapsilosis* (18%), *C. albicans* (12%), *C. glabrata* (12%), *C. kefyr* (9%), *C. pelliculosa* (5%), and *C. krusei* (5%).[21] In another recent study from North India, *C. tropicalis* (38.2%) was the most common *Candida* spp., followed by *C. pelliculosa* (16.4%), and *C. albicans* (12.7%).[20] In our study, we have not reported *C. kefyr*, although our percentage isolation of *C. pelliculosa* and *C. albicans* was similar. In contrast, in a study from South India, *C. parapsilosis* was the predominant pathogen among children.[24]

Table 3: Distribution of *Candidemia* in southern India, 2010 to 2019, according to species, and age-group

	No. (%) of isolates in each age group				
Species	*Neonate (birth to <1 month)*	*Infant (1 month to <2 years)*	*Children (2 to <12 years)*	*Adolescent (12–16 years)*	*Total no. (%)*
C. tropicalis	7 (22.6)	10 (23.8)	3 (16.7)	2 (40%)	22 (23)
C. parapsilosis	2 (6.4)	6 (14.3)	6 (33.3)	1 (20%)	15 (15.6)
C. pelliculosa	7 (22.6)	6 (14.3)	2 (11.1)	0	15 (15.6)
C. albicans	5 (16.1)	7 (16.7)	1 (5.5)	0	13 (13.6)
C. krusei	4 (12.9)	3 (7.14)	0	0	7 (7.3)
C. species non-*albicans* spp.	0	3 (7.14)	1 (5.5)	1 (20%)	5 (5.2)
C. haemulonii	2 (6.4)	2 (4.8)	0	1 (20%)	5 (5.2)
C. lipolytica	3 (9.8)	0	0	0	3 (3.1)
C. famata	0	1 (2.4)	2 (11.1)	0	3 (3.1)
C. glabrata	0	1 (2.4)	1 (5.5)	0	2 (2.1)
C. guilliermondii	0	1 (2.4)	1 (5.5)	0	2 (2.1)
C. lusitaniae	1 (3.2)	1 (2.4)	0	0	2 (2.1)
C. utilis	0	1 (2.4)	1 (5.5)	0	2 (2.1)
Total	31 (32.3)	42 (43.8)	18 (18.8)	5 (5.2%)	96

Table 4: Demographics and clinical characteristics of 96 patients with Candidemia

Characteristics	*No. (%)*
Male	64 (66.7)
Female	32 (33.3)
Congenital malformations	26 (27)
Hematological malignancy	13 (13.5)
Lung disease	9 (9.4)
Prematurity	8 (8.3)
Surgery	7 (7.3)
Septic shock	6 (6.3)
Neonatal sepsis	6 (6.3)
Low birth weight	4 (4.2)
Low APGAR score	3 (3.1)
Other medical condition	3 (3.1)
Cardiovascular disease	2 (2.1)
Hemodialysis	2 (2.1)
Renal failure	2 (2.1)
Trauma	2 (2.1)
IUGR	2 (2.1)
Fever seizure	2 (2.1)
Respiratory distress	2 (2.1)
Diabetes mellitus	1 (1)
Solid malignancy	1 (1)

Table 5: Number of expired patients in each category of *Candida* spp

Species	*Total no. of isolates*	*Total no. expired (%)*
C. pelliculosa	15	7 (23.3)
C. tropicalis	22	6 (20)
C. parapsilosis	15	5 (16.7)
C. albicans	13	3 (10)
C. haemulonii	5	3 (10)
C. famata	3	1 (3.3)
C. species non-*albicans* spp.	5	1 (3.3)
C. guilliermondii	2	1 (3.3)
C. krusei	7	0
C. lipolytica	3	0
C. glabrata	2	0
C. lusitaniae	2	0
C. utilis	2	0
Total no (%)	96	30 (31.3)

Table 6: Number of expired patients of Candidemia in each location and age-group

	Total no. of isolates	*No. of expired patients (%)*
ICU	71	24 (33.8)
IP	14	4 (28.6)
OP	11	2 (18.2)
Neonate	31	9 (29)
Infant	42	10 (23.8)
Children	18	7 (39)
Adolescent	5	4 (80)

We found statistically significant trend overtime regarding the distributions of *C. pelliculosa* and *C. famata*. In a review article comparing the overall distribution of isolates recovered from US vs non-US study sites, a difference was observed in the proportions of *Candida* species. Although it was observed that *C. albicans* was the most common species isolated overall, it accounted for a lower percentage of all isolates in non-US sites when compared to US sites. In contrast, *C. guilliermondii* was recovered more frequently in non-US study sites, while *C. krusei* was isolated in larger proportion in US than in non-US study sites.[3] *C. krusei* in our study was 7.3%.

A rarely encountered *Candida* species that has received worldwide attention as causing invasive infections is *C. auris*. This is commonly misidentified as *C. haemulonii* by commercial methods of clinical diagnosis.[16,25] Although we have not reported *C. auris* in our study, the overall *C. haemulonii* isolation was 5.2% in the pediatric age-group.

We identified low prevalence of *C. lipolytica* (3.1%), *C. famata* (3.1%), *C. glabrata* (2.1%), *C. guilliermondii* (2.1%), *C. lusitaniae* (2.1%), and *C. utilis* (2.1%) in our study as seen in other settings and geographical regions.[14,26–28] Moreover, although *C. glabrata* remained relatively uncommon in our study (2.1%), the proportion of invasive *Candida* infections caused by *C. pelliculosa* increased from 9.1% in 2010 to 2014 to 24.3% in 2015 to 2019. *C. pelliculosa* is considered a rare non-*C. albicans* spp. pathogen. Despite being uncommon, the role of this pathogen causing outbreaks has been reported in children.[4,15,29,30] Similarly, *C. glabrata* in another study has reported increase from 2.6% in 2003 to 23.7% in 2012.[12]

There were significant differences in *Candida* spp. among different locations in the healthcare setting. Majority of the isolates (74%) are from ICU, with *C. tropicalis* (18/22, 81.8%), *C. pelliculosa* (15/15, 100%), and *C. albicans* (10/13, 76.9%) as the most frequently isolated *Candida* species. It is noteworthy that uncommon *Candida* species, *C. pelliculosa*; *C. lipolytica*, *C. lusitaniae*, and *C. utilis*, were only isolated from ICU except *C. guilliermondii*.

Significant differences in *Candida* spp. were observed among different age-groups in children. In our study, we have demonstrated both *C. tropicalis* and *C. pelliculosa* (22.6%) as the predominant species in the neonates, whereas *C. albicans* was only 16.1% among the neonates compared to 13.6% in the overall pediatric group. Among the infants, we found *C. tropicalis* (23.8%) followed by *C. albicans* (16.7%). Candidemia was infrequent in adolescents with 5 cases among 96 patients. In a study from Chile, neonates had the highest proportion of cases of *C. albicans* (60%) compared to 37.3% in the overall pediatric group.[31] In a review article by Warris A, it has been mentioned that the vast majority of the infections caused by *Candida* species in the pediatric population were due to *C. albicans* or *C. parapsilosis* and *C. krusei* was less prevalent.[25] Similar finding was seen in a nationwide surveillance study in Mexico.[23]

The median age was 2 years (range, 7 days to ≤16 years), whereas the median patient age in another study was 50 months (range, 6 months to ≤18 years).[32] Candidemia was seen to be more prevalent in male with 66.7% of infected children than female with 33.3%. It corroborates with another study on pediatric candidemia where 55.4% patients infected were males and 44.6% were female.[32] However, this observation is not much in agreement with other studies reporting female predominance.[21]

In a study among the European pediatric population, cancer/allogeneic hematopoietic stem cell transplantation (43%) and congenital malformations/syndromes (21%) were the predominant

Table 7: *In vitro* antifungal susceptibilities of 94 isolates of *Candida* species to fluconazole, amphotericin B, voriconazole, flucytosine, caspofungin, and micafungin as determined by using the VITEK-2 system

Species (no. of isolates)	*Agents (no. available for susceptibilities)*	*MIC (μg/mL) range*	*MIC_{50} (μg/mL)*	*MIC_{90} (μg/mL)*	*Percentage sensitive*
C. tropicalis (22)	FLU (22)	≤1–16	≤1	2	95.5
	AMB (22)	≤0.25–1	0.5	0.5	100
	VOR (22)	≤0.12–1	≤0.12	≤0.12	100
	FC (22)	≤1–32	≤1	≤1	95.2
	CAS (12)	≤0.12–0.25	0.25	0.25	100
	MIC (8)	≤0.06	≤0.06	≤0.06	100
C. parapsilosis (15)	FLU (15)	≤0.5–2	1	2	100
	AMB (15)	≤0.25–1	0.5	0.5	100
	VOR (15)	≤0.12	≤0.12	≤0.12	100
	FC (15)	≤1	≤1	≤1	100
	CAS (12)	≤0.12–1	0.25	1	100
	MIC (8)	0.25–0.5	0.5	0.5	100
C. pelliculosa (15)	FLU (15)	≤1–8	2	4	66.7
	AMB (15)	≤0.25–0.5	0.5	0.5	
	VOR (15)	≤0.12–0.25	≤0.12	0.25	
	FC (15)	≤1	≤1	≤1	100
	CAS (11)	≤0.12–0.25	0.25	0.25	
	MIC (10)	≤0.06–0.12	≤0.06	0.12	
C. albicans (13)	FLU (13)	≤1–8	≤1	2	100
	AMB (13)	≤0.25–1	1	1	100
	VOR (13)	≤0.12	≤0.12	≤0.12	100
	FC (13)	≤1–≥64	≤1	≥64	92.3
	CAS (3)	≤0.12	≤0.12	≤0.12	100
	MIC (3)	≤0.06	≤0.06	≤0.06	100
C. krusei (*n* = 7)	FLU (7)	≥4–64	8	≥64	Intrinsically resistant
	AMB (7)	≤0.25–4	1	4	71.4
	VOR (7)	≤0.12–0.5	≤0.12	0.5	100
	FC (7)	4–16	8	16	14.3
	CAS (4)	≤0.12–0.5	0.25	0.5	75
	MIC (2)	0.12	0.12	0.12	100
C. haemulonii (*n* = 5)	FLU (5)	16–32	16	32	0
	AMB (5)	2–≥16	8	≥16	
	VOR (5)	≤0.12–8	≤0.12	8	
	FC (5)	≤1	≤1	≤1	100
	CAS (5)	≤0.12–0.5	≤0.12	0.5	
	MIC (5)	≤0.06–0.12	≤0.06	0.12	
Candida species non-*albicans* (3)	FLU (3)	2–8	8	8	33.3
	AMB (3)	0.5–≥16	0.5	≥16	
	VOR (2)	≤0.12	≤0.12	≤0.12	
	FC (3)	≤1	≤1	≤1	100
	CAS (1)	0.5	0.5	0.5	
	MIC (1)	0.5	0.5	0.5	
C. lipolytica (3)	FLU (3)	4–16	8	16	0
	AMB (3)	0.5–1	0.5	1	
	VOR (3)	≤0.12–0.25	≤0.12	0.25	
	FC (3)	4–8	8	8	33.3
	CAS (2)	≤0.12	≤0.12	≤0.12	
	MIC	–	–	–	

Contd…

Contd…

Species (no. of isolates)	*Agents (no. available for susceptibilities)*	*MIC (µg/mL) range*	*MIC_{50} (µg/mL)*	*MIC_{90} (µg/mL)*	*Percentage sensitive*
C. famata (3)	FLU (3)	≤0.5–4	≤0.5	4	66.7
	AMB (3)	≤0.25	≤0.25	≤0.25	
	VOR (2)	≤0.12	≤0.12	≤0.12	
	FC (3)	≤1	≤1	≤1	100
	CAS (1)	≤0.12–0.25	0.25	0.25	
	MIC (1)	0.12–0.25	0.12	0.25	
C. glabrata (2)	FLU (1)	2	2	2	100
	AMB (2)	0.5–1	0.5	1	100
	VOR (1)	0.25	0.25	0.25	
	5-FC (1)	≤1	≤1	≤1	100
	CAS (1)	≤0.12	≤0.12	≤0.12	100
	MIC (2)	≤0.06	≤0.06	≤0.06	100
C. guilliermondii (2)	FLU (2)	2–4	2	4	50
	AMB (2)	≤0.25	≤0.25	≤0.25	100
	VOR (2)	≤0.12	≤0.12	≤0.12	
	FC (1)	≤1	≤1	≤1	100
	CAS (1)	0.5	0.5	0.5	100
	MIC (1)	0.5	0.5	0.5	100
C. lusitaniae (2)	FLU (2)	≤1	≤1	≤1	100
	AMB (2)	0.5	0.5	0.5	
	VOR (2)	≤0.12	≤0.12	≤0.12	
	FC (2)	≤1	≤1	≤1	100
	CAS (1)	1	1	1	
	MIC	–	–	–	
C. utilis (2)	FLU (2)	≤1–2	≤1	2	100
	AMB (2)	≤0.25–0.5	≤0.25	0.5	
	VOR (2)	≤0.12	≤0.12	≤0.12	
	FC (2)	≤1	≤1	≤1	100
	CAS (2)	≤0.12	≤0.12	≤0.12	
	MIC (2)	≤0.06–0.12	≤0.06	0.12	
Total (94)	FLU (93)	≤0.5–≥64	1	8	71
	AMB (94)	≤0.25–≥16	0.5	1	91.5
	VOR (91)	≤0.12–8	≤0.12	0.25	99
	FC (92)	≤1–≥64	≤1	8	87.8
	CAS (56)	≤0.12–1	≤0.25	0.5	94
	MIC (43)	≤0.06–0.12	0.5	0.12	100

Flu: Fluconazole; AMB: Amphotericin B; VOR: Voriconazole; FC: Flucytosine; CAS: Caspofungin; MIC: Micafungin

underlying conditions.[28] This is similar to our study with congenital malformation reported in 27% and hematological malignancy in 13.5% as the two predominant predisposing conditions. In our study, there were probably not enough patients with risk factors to draw any firm conclusion.

The overall mortality was found to be 31.3% in our study which is significantly higher than a study in Turkey (13.7%) and Denmark (10.2%).[7,33] In another study, overall mortality was found to be 41%.[9] The highest mortality was seen in *C. pelliculosa* (23.3%), followed by *C. tropicalis* (20%), *C. parapsilosis* (16.7%), *C. albicans* (10%), and *C. haemulonii* (10%). In another study in a PICU, *C. albicans* was found to have the highest mortality rate among all *Candida* species (30.7%)[7] In a Scottish study, mortality was primarily associated with *C. albicans*. (49%), followed by *C. glabrata* (32%), *C. parapsilosis* (11.3%), and other species (7.7%).[9] When compared to adults, there was no apparent difference seen in mortality between *C. albicans* and non-*C. albicans* BSIs in our study which is similar to other reports in pediatric age-groups.[32,34,35] Candidemia among children admitted in ICU was associated with higher mortality (33.8%) in comparison to children admitted in wards (28.6%). This finding is consistent with a review article on pediatric invasive candidiasis and another study among adults in a tertiary care Saudi hospital.[3,10] In our study, mortality was found to be highest in 12 to 16-years age-group (80%) followed by in 2 to <12 years (39%). This conclusion may not be clinically relevant as the total numbers in each category was less. In a nationwide cohort study from Denmark, the mortality was found to be highest for neonates (17.1%).[33]

Most of the *Candida* spp. worldwide was found to be sensitive to polyene and echinocandins.[12,13,36] *C. parapsilosis* remains 100% sensitive to all the tested antifungals in our study followed

by *C. albicans*, 100 % sensitive to all except flucytosine (92.3%), *C. tropicalis*, 100 % sensitive to all except fluconazole (95.5%), and flucytosine (95.2%). It was found that micafungin was the only antifungal that had 100% overall sensitivity to all *Candida* spp. followed by voriconazole 99%. Our susceptibility data were similar to a surveillance study of candidemia in Scotland, with limited or no resistance found among *C. albicans*, *C.parapsilosis*, or *C. tropicalis* isolates.[9] In the present study, the fluconazole sensitivity was 71% for *Candida* spp. The increase in fluconazole resistance is a matter of deep concern in disseminated candidiasis involving candidemia.[21,37,38] This could be due to extensive use of fluconazole in various clinical conditions which also has led to dominance of non-*C. albicans* species over *C. albicans*.[39] Clinicians should also keep in mind about intrinsic resistance of *C. krusei* isolates to fluconazole and decreased susceptibility to other antifungals. Hence speciation and susceptibility testing of all clinical isolates of candidemia is of utmost importance.

Only 75% of *C. krusei* were susceptible to caspofungin. This is similar to a study where they have reported 66.7% of *C. krusei* isolates susceptible to caspofungin, in contrast to another study where the *C. krusei* showed 100% sensitivity to caspofungin.[12,21]

Limitations

The findings in this report are subject to certain limitations. The underlying conditions and predisposing factors in our study were extracted from hospital information system, which might have resulted in underestimates of certain conditions, if not entered in the information system due to busy schedule of the healthcare workers. In addition, the underestimates of true proportion of invasive candidiasis could be due to difficulty in obtaining adequate blood sample volume as per the age of the children recommended in the automated culture bottles. It is a common practice among the clinicians to obtain only one blood culture bottle instead of multiple sets, probably to minimize the treatment cost to the patient. It is an established fact that the blood volume plays an important role in the optimal sensitivity of the automated blood culture system. The number of days before the episode of candidemia, antifungal treatment and length of stay in our study could not be evaluated.

Conclusion

Candidemia remains one of the serious causes of illness and death worldwide. Uncommon *Candida* species have emerged as causative agents of invasive fungal infections among children.

These pathogens frequently have shown decreased susceptibility to fluconazole, the most frequently used antifungals. Therefore, surveillance data for candidemia should continue to monitor incidence trends by age, species distribution, changes in underlying predisposing factors, track emergence of resistance, and assess trends in antifungal treatment. Finally, understanding the epidemiology of *Candida* spp. is critical as it is expected to improve the development of treatment, outcome and preventive efforts.

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