

Prevalence of *Candida* blood stream infections among children in tertiary care hospital: detection of species and antifungal susceptibility

This article was published in the following Dove Press journal:
Infection and Drug Resistance

Sahar Mohammed Khairat¹
Amal Mohammed Sayed¹
Mohammad Nabih²
Noha Salah Soliman³
Yosra Mohammed Hassan³

¹Department of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, Giza, Egypt; ²Department of Pediatrics, Faculty of Medicine, Cairo University, Giza, Egypt; ³Department of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, Giza, Egypt

Background: Of all blood stream infections (BSI), candidaemia poses the greatest threat with a high fatality rate among children. There has been an increase in the number of reports of non-*C. albicans* species and antifungal resistance has progressively emerge.

Aim: The present study aimed to demonstrate the prevalence of candidaemia among children and to characterize the involved species and their susceptibility to antifungal agents.

Methodology: Microbes were isolated from blood samples and identified via standard microbiological procedures. Chromogenic media was used to characterize the *Candida* species. The susceptibility of the isolates to the antifungal agents; caspofungin, amphotericin, itraconazole, and fluconazole was determined with the E-test.

Statistical methods: The data were analysed with Statistical Package for the Social Science SPSS; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows. Comparisons between the study groups were performed using the Chi square (χ^2) test. *p*-values less than 0.05 were considered significant.

Results: Candidaemia accounted for 17.3% of all BSIs. *C. albicans* and non-*C. albicans* species accounted for 36% and 64% of the cases of candidaemia, respectively. Caspofungin, amphotericin, itraconazole, and fluconazole antifungals had activities of 99%, 97%, 73% and 64%, respectively. In total, 64% of patients with candidaemia died.

Conclusion: The prevalence of candidaemia was high, the fatality rate was alarming and non-*C. albicans* species were predominant. Fluconazole was the least effective of the tested antifungal agents owing to the high level of resistance.

Keywords: candidaemia, chromogenic agar, antifungal

Introduction

Invasive candidiasis is a life-threatening condition that endangers critically ill patients and is associated with a high fatality rate. The mortality rate is unacceptably high, ranging from 29% to 76%.¹ Neonates, elderly patients and those admitted to intensive care units (ICUs) are at greater risk of death than other categories of patients.² Candidaemia is defined as the presence of *Candida* species in the blood determined by at least one positive blood culture in patients with fever and signs of a blood stream infection (BSI).³

Reports of *Candida* BSIs have significantly increased worldwide over the past 20 years. *Candida* BSIs are the fourth most common type of nosocomial BSIs in the USA and they are the sixth most common in Europe.^{1,4}

Correspondence: Yosra Mohammed Hassan
Department of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, 24 Abd ElRahman AlBarkouki Street - Al Manial, Cairo 11555, Egypt
Email yosran3@gmail.com

The World Health Organization (WHO) and the Joint United Nations Program on HIV/AIDS (UNAIDS) reported that in 2011, there were 4,127 cases of candidaemia in the total population of 82,500,000.⁵ Immunosuppression, prolonged antibiotic intake, inserted devices, extreme age and ICU admission are all predictive risk factors for invasive candidiasis.⁶

Several studies have reported a change in the type of *Candida* isolated from blood, with an increasing prevalence of non-*C. albicans* species.⁷ *C. tropicalis* and *C. krusei* are commonly observed in leukaemic and neutropenic patients. *C. parapsilosis* causes 30% of candidaemia cases among new-borns and 10–15% of cases among adults.⁸

The emergence of antifungal resistance among *Candida* species is considered a leading cause of therapeutic failure and the high mortality rate. The present work aimed to calculate the prevalence of candidaemia among pediatric patients, identify the risk factors, characterize the involved species and determine the susceptibility of the isolated strains to antifungal agents, specifically caspofungin, amphotericin B, itraconazole and fluconazole.

Methodology

This study was conducted with positive blood cultures from children suspected of having BSIs in tertiary pediatric hospitals of Cairo University -2017.

Clinical data

The clinical characteristics of the patients with blood cultures positive for *Candida* were collected including; the hospital site, history of previous administration of antibiotics, associated indwelling devices, factors affecting immunosuppression and 30-day mortality after the diagnosis of *Candida* BSI. The clinical data were retrieved from the electronic medical records and the associated request form of routine patients' samples delivered to the laboratory. A written informed consent was obtained by the parents or legal guardians of the patients, and the study was conducted in accordance with the Declaration of Helsinki. The study was reviewed by the Research Ethics Committee (REC) of the Clinical Pathology department at the Faculty of Medicine, Cairo University for all the required ethical statements and was approved with an ID code: I-201008.

Growth detection and species identification

The blood samples were delivered to the laboratory in pediatric blood culture bottles and microbial growth was

detected by measuring the signal production with an automated Bact/Alert system (*Biomerieux, Craaponne, France*).

Subculturing of the positive blood cultures was performed on blood, chocolate and MacConkey agar (*Oxoid, England*) to isolate bacteria and on Sabouraud dextrose medium (*BioMérieux, France, REF 43 651*) to isolate fungi.^{9,10} The primary differentiation of the isolated *Candida* species into *C. albicans* and non-*C. albicans* species was determined by germ tube test.¹¹ Further characterization of the *Candida* species was performed by subculturing on chromogenic *Candida* agar, which discriminates among different *Candida* species by color (*Oxoid, England, REF: CM1002B*).¹⁰ All *Candida* isolates were stored in glycerol broth at -80°C .

Antifungal susceptibility testing

Candida isolates were tested for their susceptibility to 4 antifungals; namely, itraconazole, fluconazole, amphotericin B and caspofungin; through the detection of the minimal inhibitory concentrations (MICs) with E-test strips (*bioMérieux*) and GM-MH agar (Mueller-Hinton agar containing 2% glucose and methylene blue 5 microg/mL).⁹ As reported by Lee et al, 2009, the results of the E-test with the GM-MH agar plate are strongly correlated with the results of the antifungal macrodilution susceptibility test.¹² The MICs for the antifungals were interpreted according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI M27-S4) *CLSI, 2012*.¹³ According to CLSI M27-S4, the sensitive and resistant MICs for *C. albicans* and *C. tropicalis* are (≤ 2 and ≥ 8) $\mu\text{g/ml}$ for fluconazole, (≤ 0.125 and ≥ 0.5) $\mu\text{g/ml}$ for itraconazole and (≤ 0.25 and ≥ 1) $\mu\text{g/ml}$ for caspofungin. For *C. krusei*, sensitive and resistant MICs are (≤ 0.125 and ≥ 0.5) $\mu\text{g/ml}$ for itraconazole and (≤ 0.25 and ≥ 1) $\mu\text{g/ml}$ for caspofungin. The European Committee on Antimicrobial susceptibility testing (EUCAST) guidelines were followed for amphotericin B; the MICs for which have not been defined by the CLSI.¹⁴

Quality control with reference strains

The reference strains *C. albicans* ATCC 90028, *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 were used to ensure the quality of antifungal susceptibility tests.¹⁴

Statistical methods

Data were statistically analysed with Statistical Package for the Social Science (SPSS; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows. Comparisons

between the study groups were made with the Chi square (χ^2) test. p -values less than 0.05 were considered significant.

Results

Among the 1934 pediatric blood cultures sent to the microbiology laboratory in 2017, 578 (29.8%) were positive for different microorganisms; with 100/578 (17.3%) positive for *Candida*.

A history of previous antibiotic intake for >2 weeks was observed in 75% (75/100) of candidaemia cases. The antibiotics are listed in Figure 1. Immunosuppression was detected in 35 cases in the form of neutropenia (18), steroid intake (10) and both neutropenia and steroid intake (7). The isolated *Candida* species are shown in Figure 2; these isolates were from ICUs and wards in 59% and 41% of the cases, respectively, as shown in Table 1.

The ages of the enrolled patients with candidaemia ranged from birth to 12 years, and they were categorized into the following age groups: 0–28 days (35), >28 days–2 years (41), >2–6 years (22) and >6–12 years (2).

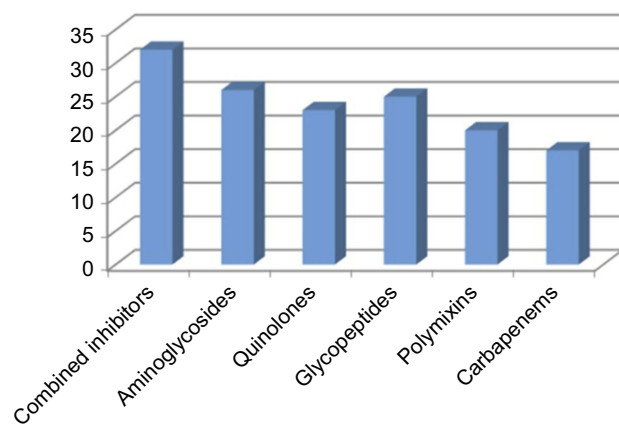


Figure 1 History of previous antibiotic intake prior to candidaemia. Combined inhibitors: β lactam- β lactamase inhibitors (Ampicillin –Sulbactam, Piperacillin-Tazobactam).

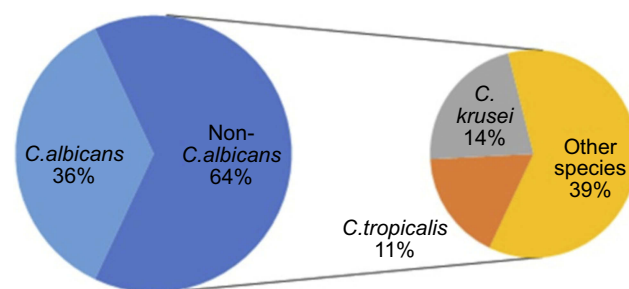


Figure 2 Different *Candida* species isolated from blood.

Indwelling medical devices were observed in 83% of candidaemia cases, with multiple devices sometimes found to a single patient, especially in the ICU. The *Candida* species isolated from patients with devices are shown in Table 2.

The susceptibility of *C. albicans* to the 4 tested anti-fungals is shown in Table 3; caspofungin and amphotericin were the most efficacious, itraconazole and fluconazole were the least efficacious. The MICs for fluconazole, itraconazole and amphotericin B for *C. parapsilosis* ATCC 22019 ranged from 1 to 4 $\mu\text{g/mL}$, from 0.12 to 0.5 $\mu\text{g/mL}$, and from 0.5 to 1 $\mu\text{g/mL}$, respectively; for *C. albicans* ATCC 90028 the MICs ranged from 0.125 to 0.5 $\mu\text{g/mL}$, from 0.064 to 0.25 $\mu\text{g/mL}$, and from 0.125 to 0.5 $\mu\text{g/mL}$, respectively and for *C. krusei* ATCC 6258 the MICs ranged from 16 to 128 $\mu\text{g/mL}$, from 0.25 to 1 $\mu\text{g/mL}$, and from 1 to 4 $\mu\text{g/mL}$, respectively; which were all meeting the expected ranges according to the required guidelines by the Clinical and Laboratory Standards Institute.

The descriptive analysis of the MICs is shown in Table 4, with the lowest MIC values were recorded for itraconazole with *C. krusei* with a susceptible range of (0.0–0.09); for *C. albicans* with amphotericin, with a susceptible range of (0.0–0.019); and *C. tropicalis* and other non-*C. albicans* species with caspofungin, with susceptible ranges of (0.01–0.05) and (0.01–0.8), respectively.

After excluding the 14 intrinsically resistant *C. krusei* isolates, fluconazole resistance was recorded in 41.8% (36/86) of the *Candida* isolates; with resistance found in 52.8% and 47.2% of isolates from patients in ICUs and in wards, respectively. Fluconazole resistant *C. albicans* and non-*C. albicans* species accounted for 38.9% and 44% of the total, respectively. As shown in Table 5, devices were found in 88.9% of patients with fluconazole-resistant isolates. Previous fluconazole intake was present in 19.4% (7/36) of fluconazole-resistant cases. In total, 64% (64/100) of patients diagnosed with *Candida* BSI died within 30 days; the descriptive analysis is shown in Table 6. Fluconazole resistance was detected in 34.4% of the deceased patients with *Candida* BSI.

Discussion

Candida BSIs pose a serious threat, especially to vulnerable patients. In the present study, candidaemia accounted for 100 of the 578 confirmed BSIs with a prevalence of 17.3%. Other studies in Egypt reported candidaemia prevalences of 16% and 19% among pediatric ICU patients with BSIs.^{15,16} A higher prevalence of candidaemia (38%)

Table 1 Distribution of *Candida* species in different wards and ICUs

Wards & ICUs		Candida species							
		Non- <i>C. albicans</i> (64)							
		<i>C. albicans</i> (n=36)		<i>C. tropicalis</i> (n=11)		<i>C. krusei</i> (n=14)		Other species (n=39)	
		No.	%	No.	%	No.	%	No.	%
ICUs	ER	7 (19.4%)	2	18.2	6	42.9	15	38.5	
	SICU	2 (5.6%)	0	0.0	1	7.1	1	2.6	
	NICU	3 (8.3%)	3	27.3	0	0.0	3	7.7	
	ICU	9 (25.0%)	1	9.1	1	7.1	2	5.1	
	CTICU	1 (2.8%)	0	0.0	0	0.0	0	0.0	
	CICU	2 (5.6%)	0	0.0	0	0.0	0	0.0	
	Total	24 (66.7%)	6	54.6	8	57.1	21	53.8	
		35 (54.7%)							
Wards	Cardiothoracic	4 (11.1%)	3	27.3	3	21.4	9	23.1	
	Neonate	5 (13.9%)	2	18.2	3	21.4	7	17.9	
	Neurosurgery	2 (5.6%)	0	0.0	0	0.0	0	0.0	
	Dialysis	1 (2.8%)	0	0.0	0	0.0	0	0.0	
	Surgery	0	0	0.0	0	0.0	2	5.1	
	Total	12 (33.3%)	5	45.5	6	42.9	18	46.2	
		29 (45.3%)							

Abbreviations: SICU, surgical intensive care unit; NICU, neonatal intensive care unit; ER, emergency unit; ICU, intensive care unit; CTICU, cardio thoracic intensive care unit; CICU, cardiology intensive care unit.

Table 2 Associated indwelling devices with candidaemia

Device	Candidaemia (n=100)				p-value
	<i>C. albicans</i> (n=36)		Non- <i>C. albicans</i> (n=64)		
	No.	%	No.	%	
CVL	25	69.4	39	60.9	0.395
Urinary catheter	14	38.9	18	28.1	0.268
Ventilator	21	58.3	28	43.8	0.161
Gastric tube	20	55.6	31	48.4	0.494
Prosthetic valve	3	8.3	5	7.8	^{FE} p=1.000

Note: ^{FE}p, p-value for Fisher Exact for Chi square test.

Abbreviation: CVL, central venous line.

was reported in another study conducted with a different study populations of adult patients in internal medicine wards.¹⁷

The results of the present study agreed with those of another Egyptian study, which reported a predominance of non-*C. albicans* species (60% non-*C. albicans* versus 40% *C. albicans*).¹⁵ This finding was consistent with the results

of a study that reported *C. albicans* and non-*C. albicans* BSIs in the neonatal ICU of Child Healthcare, with prevalences of 43.5% vs 56.5%, respectively.¹⁸ Several studies also reported this pattern in contrast to the results of older published.^{6,16,19,20}

Another study conducted in Egypt also found that *C. tropicalis* was the second common non-*C. albicans*

Table 3 Results of antifungal susceptibility testing among blood stream isolated *Candida*

<i>Candida</i> species		Fluconazole		Amphotericine		Itraconazole		Caspofungin		
		S	R	S	R	S	R	S	R	
<i>C. albicans</i> (n=36)		No.	22	14	34	2	22	14	35	1
		%	61.1	38.9	94.4	5.6	61.1	38.9	97.2	2.8
Non- <i>C. albicans</i> (n=64)	Total	No.	28	22	63	1	51	13	64	0
		%	56**	44**	98.4	1.5	79.6	20.3	100	0
	<i>C. tropicalis</i> (n=11)	No.	6	5	11	0	9	2	11	0
		%	54.5	45.5	100.0	0.0	81.8	18.2	100.0	0.0
	<i>C. krusei</i> * (n=14)	No.	-	-	14	0	8	6	14	0
		%	-	-	100.0	0.0	57.1	42.9	100.0	0.0
	Other species (n=39)	No.	22	17	38	1	34	5	39	0
		%	56.4	43.5	97.4	2.6	87.2	12.8	100.0	0.0

Notes: **C. krusei* is intrinsically resistant; **Fluconazole resistance was calculated out of 50 non-*C. albicans*, after exclusion of 14 intrinsically resistant *C. Krusei*.

Table 4 The descriptive analysis of susceptible MIC values to antifungals

<i>Candida</i> species	Antifungal agents	MIC values ($\mu\text{g ml}^{-1}$)		
		Range	Mean \pm SD.	Median
<i>C. albicans</i>	Fluconazole (n=22)	0.02–1.50	0.83 \pm 0.65	1.0
	Amphotericin (n=34)	0.0–0.19	0.05 \pm 0.04	0.03
	Itraconazole (n=22)	0.0–0.50	0.07 \pm 0.10	0.05
	Caspofungin (n=35)	0.0–0.44	0.05 \pm 0.08	0.02
<i>C. tropicalis</i>	Fluconazole (n=11)	0.16–1.50	0.86 \pm 0.54	0.75
	Amphotericin (n=11)	0.01–0.32	0.10 \pm 0.11	0.05
	Itraconazole (n=9)	0.02–0.38	0.08 \pm 0.11	0.04
	Caspofungin (n=11)	0.01–0.05	0.02 \pm 0.01	0.01
<i>C. krusei</i>	Amphotericin (n=14)	0.02–0.13	0.06 \pm 0.03	0.06
	Itraconazole (n=8)	0.0–0.09	0.04 \pm 0.03	0.04
	Caspofungin (n=14)	0.01–0.09	0.03 \pm 0.02	0.02
Other species	Fluconazole (n=22)	0.0–1.50	0.72 \pm 0.61	1.0
	Amphotericin (n=38)	0.0–1.0	0.07 \pm 0.16	0.05
	Itraconazole (n=34)	0.01–0.50	0.07 \pm 0.11	0.03
	Caspofungin (n=39)	0.01–0.80	0.05 \pm 0.13	0.02

Note: The MICs for fluconazole, itraconazole and amphotericin B for *C. parapsilosis* ATCC 22,019 ranged from 1 to 4 $\mu\text{g/mL}$, from 0.12 to 0.5 $\mu\text{g/mL}$, and from 0.5 to 1 $\mu\text{g/mL}$, respectively; for *C. albicans* ATCC 90,028 the MICs ranged from 0.125 to 0.5 $\mu\text{g/mL}$, from 0.064 to 0.25 $\mu\text{g/mL}$, and from 0.125 to 0.5 $\mu\text{g/mL}$, respectively and for *C. krusei* ATCC 6258 the MICs ranged from 16 to 128 $\mu\text{g/mL}$, from 0.25 to 1 $\mu\text{g/mL}$, and from 1 to 4 $\mu\text{g/mL}$, respectively; which were all meeting the expected ranges according to the required guidelines by the Clinical and Laboratory Standards Institute.

species isolated with a prevalence of 17%; the prevalence rates of *C. tropicalis* in other studies were 14.8% and 9.6%.^{16,19,21} However, those studies; reported *C. parapsilosis* as the most common non-*C. albicans* species isolated, while *C. krusei* was the most common species in the present study.

In the present study, candidaemia was most commonly identified in patients in the ICU (59%) and in neonates (35%), which was consistent with the findings of another study.²² Other studies found fewer patients with candidaemia in ICUs which might be due to more strict adherence to infection control measures.^{21,23}

Table 5 The association of Fluconazole resistance with indwelling devices

Device		Fluconazole				p-value
		S (n=64)		R (n=36)		
		No.	%	No.	%	
No associated devices		13	20.3	4	11.1	0.240
Associated devices		51	79.7	32	88.9	
Types	CVL	36	56.3	28	77.8	0.031*
	Urinary catheter	19	29.7	13	36.1	0.509
	Ventilator	30	46.9	19	52.8	0.571
	Ryle	30	46.9	21	58.3	0.271
	Prosthetic valve	4	6.3	4	11.1	^{FE} p=0.454

Notes: ^{FE}p, p-value for Fisher Exact for Chi square test for comparing between the two groups. *Statistically significant at p≤0.05.

Table 6 Descriptive analysis of developed mortality among candidaemia cases

Mortality among candidaemia (n=64)			
		No.	%
Age (years)			
0–28 days		21	32.8
>28 days–2 years		31	48.4
>2–6 years		11	17.2
>6–12 years		1	1.6
Fluconazole			
Sensitive		42	65.6
Resistant		22	34.4
C. albicans		22	34.4
Non-C. albicans	<i>C. tropicalis</i>	6	9.4
	<i>C. krusei</i>	8	12.5
	Other species	28	43.8
	Total	42	65.6

The findings of the present study were compatible with those of other studies with regard to the risk factors for candidaemia; the most important risk factor was previous exposure to antibiotics for >14 days, followed by the presence of a central venous line, and *C. albicans* was more commonly isolated than non- *C. albicans* species.^{20,23}

With regards to antifungal resistance, 3% of the isolates were resistant to amphotericin; which was consistent with the results of another study (6.9%). This resistance was due to prior extensive use of amphotericin B in immunocompromised patients, unlike in other studies

that reported no amphotericin B resistance.^{23–25} The present study showed that 27% of the isolates, mostly *C. albicans* and not *C. tropicalis* were resistant to itraconazole resistance; which agreed with some of the previous studies.^{24,25} Caspofungin resistance rates remained low; the present study found that 1% of the isolates were resistant to caspofungin.²⁶

The rate of fluconazole resistance was 41.8%, and more non- *C. albicans* species were resistant than *C. albicans* species (44% versus 38.9%). A higher rate of fluconazole resistance was found in *C. tropicalis* than in *C. albicans*, which was similar to the results of one study (7.2% versus 1.3%), while the opposite trend was observed in another study.^{7,22}

Generally, ICUs are considered epicenters of antimicrobial resistance.^{18,20} In the present study, the majority of fluconazole-resistant isolates (52.8%) were recovered from patients in ICUs, which agreed with the findings of another study, which recovered 94% of the isolates from ICUs.²⁷

The majority of enrolled cases (64%) died within experienced 30 days of diagnosis, of whom 34.4% were resistant to fluconazole; these findings agreed with those of another study that found resistance in 41.1% of deceased cases.²⁸ Several studies reported mortality rates of 51.2% and 42.4% among patients with candidaemia.^{16,21} As in other studies, we observed higher mortality rates in patients infected with non- *C. albicans* species than in patients infected with *C. albicans* (65.6% versus 34.4%, respectively).^{20,23}

Conclusion

In the present study, candidaemia accounted for 17.3% of all BSIs among pediatric patients, with a predominance of

non- *C. albicans* species. Caspofungin had the highest antifungal activity, while fluconazole had the least. The early diagnosis of *Candida* BSI and its resistance profile are essential to improve outcomes, especially in critically ill neonates and children of preschool age.

Limitations

The lack of availability of advanced molecular techniques in the present study limited the ability to identify the genetic basis of the antifungal resistance and the determination of the degree of genetic relatedness of the isolated *Candida* species. CHROM agar was challenged by lacking ability to discriminate some non-*C. albicans* species, which all give similar beige/brown/yellow colors, due to the mixture of natural pigmentation and some alkaline phosphatase enzyme activity.

Disclosure

The authors report no conflicts of interest in this work.

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