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Article

Trends in pediatric candidemia: epidemiology, antifungal susceptibility and patient characteristics in a children's hospital

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Abstract: ***Background***. *Candida* bloodstream infections (CBSIs) have decreased among pediatric populations in the United States, but remain an important cause of morbidity and mortality. Species distributions and susceptibility patterns of CBSI isolates diverge widely between children and adults. Awareness of these patterns can inform clinical decision-making for empiric or pre-emptive therapy of children at risk for candidemia. ***Methods.*** CBSIs occurring from 2006-2016 among patients in a large children's hospital were analyzed for age specific trends in incidence rate, risk factors for breakthrough-CBSI and death, as well as underlying conditions. *Candida* species distributions and susceptibility patterns were evaluated in addition to antifungal agent use. ***Results***. The overall incidence rate of CBSI among this complex patient population was 1.97/1,000 patient-days. About half of CBSI episodes occurred in immunocompetent children and 14% in Neonatal Intensive Care Unit (NICU) patients. Antifungal resistance was minimal: 96.7% of isolates were fluconazole-, 99% were micafungin-, and all were amphotericin susceptible. Liposomal amphotericin was the most commonly prescribed antifungal agent including for NICU patients. Overall CBSI-associated mortality was 13.7%; there were no deaths associated with CBSI among NICU patients after 2011. ***Conclusions***. Pediatric CBSI characteristics differ substantially from those in adults. Improved management of underlying diseases and antimicrobial stewardship may further decrease morbidity and mortality from CBSI while continuing to maintain low resistance rates among *Candida* isolates.

Keywords: Candida; bloodstream infection; pediatric; neonatal; antifungal

1. Introduction

Candida bloodstream infections (CBSI) are a leading cause of invasive fungal infections in hospitalized children, and one of the most common causes of healthcare-associated infections worldwide. While the epidemiology of invasive fungal infections, including CBSI, varies according to geographical region and patient population, globally non-albicans *Candida* species together cause the majority of CBSI, and resistant *Candida* species and strains are emerging among adult patient populations.

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While CBSI incidence in children has been decreasing in the United States over recent decades (1) as infection control and antimicrobial stewardship practices have continued to become more rigorous and universally implemented, CBSI still remain associated with high pathogen-related morbidity and mortality, increased length of hospitalization and considerable resource utilization (2-4). Some pediatric patient populations such as neonates and infants under the age of one, children with hematologic malignancies, and critically ill children in intensive care units are known to be at increased risk for CBSI, but established risk factors remain poor predictors of when and in whom CBSI occur (5). Early diagnosis is especially challenging in children given the nonspecific symptoms of candidemia and the low sensitivity of blood cultures (6). In some populations like premature neonates and neutropenic oncologic patients, empiric or pre-emptive antifungal therapy can decrease delays to initiation of appropriate therapy inevitably caused by reliance on blood culture results. Pediatric and adult populations differ with respect to prevalence of isolated *Candida* species and susceptibility patterns even in the same geographic areas (7). Surveillance of local species distribution and anti-fungal susceptibility patterns therefore aids in rational choice of empiric or pre-emptive therapy, in choices of prophylactic regimens, and in antimicrobial stewardship. The present study was undertaken to evaluate changes in epidemiology, anti-fungal susceptibility, patient characteristics and management of CBSI in a large freestanding children's hospital over an 11-year period.

2. Materials and methods

After receiving approval from the Institutional Review Board of Boston Children's Hospital (BCH), we performed a retrospective cohort study of CBSI in patients admitted at BCH between January 2006 and December 2016.

2.1. Study site

Boston Children's Hospital (BCH) is a 406-bed quaternary care children's hospital in Boston, Massachusetts with specialized units including neonatal, cardiac, medical and medical/surgical intensive care units, as well as oncology, solid organ and stem cell transplant units, which care for highly complex patient populations.

2.2. Definitions

A CBSI was defined as positive blood culture for a *Candida* species alone. A CBSI episode was defined as a positive blood culture for only a *Candida* species ≥30 days before or after another blood culture growing *Candida* (8). Polymicrobial blood cultures growing other organisms in addition to *Candida* species were not included. Breakthrough (BT)-CBSI was defined as a CBSI that occurred in patients receiving systemic antifungal agents for at least 3 days before the first positive blood culture (9). Central line-associated blood stream infection (CLABSI) was defined according to the Centers for Disease Control and Prevention (CDC) surveillance criteria (10). Recurrent CBSI was defined as a second or more episode of CBSI in the same patient, separated by at least 1 month. Patients were categorized as immunocompetent, immunocompromised, or in the neonatal intensive care unit (NICU). The latter group was considered separately because of the unique physiological immaturity of the neonatal immune system and skin barrier. Very preterm was defined as birth at less than 32 weeks of gestation and extremely preterm, defined as birth at or before 25 weeks of gestation. Mortality associated with CBSI was defined as death as a direct consequence of CBSI or death from CBSI-associated complications (3) maximally 60 days after the first positive culture as determined by 2 investigators upon chart review (A. I. P. and J. R. K.).

Primary *Candida* species identification was performed in the BCH microbiology laboratory. Blood samples were cultured in the BacT/AlerT 3D system (Biomérieux). Positive culture bottles were plated on Sabouraud Dextrose Emmons, in addition to bacteriologic agar media. Colonies growing on Sabouraud medium were examined microscopically and yeast-shaped organisms were immediately inoculated to fetal bovine serum; formation of germ tubes at 2.5-4 hours confirmed

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speciation as *Candida albicans*. Isolates that did not produce germ tubes were speciated by VITEK 2YST card and/or by API20 C AuX (Biomérieux) strip and confirmed by morphology on cornmeal agar medium. Antifungal susceptibility testing was performed at ARUP Laboratories, Salt Lake City, Utah, a commercial clinical laboratory. In vitro susceptibility to micafungin, fluconazole and voriconazole was defined by Clinical and Laboratory Standards Institute criteria, as well as using species-specific epidemiological cutoff values for less prevalent *Candida* species (11). Multi-resistance was defined as resistance to two antifungal drug classes, azoles and echinocandins.

A review of electronic medical records was performed on all patients within the study period with CBSI that met study definitions. Relevant data collected from the electronic medical records included age, underlying disease, presence of neutropenia (neutrophil count <500/mm^3), exposure to broad spectrum antibiotics (piperacillin-tazobactam, carbapenems, third and fourth generation cephalosporins, glycopeptides, aminoglycosides and fluoroquinolones) in the 7 days preceding CBSI, exposure to systemic antifungals and steroids, and antifungal agent used for treatment when CBSI was identified. The presence of a central venous catheter (CVC) and receipt of parenteral nutrition (PN) at the time of CBSI were also recorded.

2.3. Outcome measures and statistical analyses

Frequencies, percentages, and descriptive statistics were used to summarize patient characteristics and anti-fungal susceptibility overall, as well as by species of *Candida* causing CBSI. Differences in patient characteristics across species-specific CBSI were compared using the chi-square test of proportions for categorical variables and the Tukey's multiple comparison test for distribution of mean age of patients. The primary outcome was trends in incidence rate of CBSI during the study period. Secondary outcomes included (1) age-specific trends in incidence rate of CBSI, (2) Risk factors for developing breakthrough-CBSI, and (3) risk factors associated with death. We calculated CBSI rates per 1000 patient days of hospitalization for each year in the study period, and *Candida* CLABSI rates per 1000 CVC days between 2011-2016, when data on CVC days became available. Additionally, we calculated annual CBSI rates per 1000 patient days by age group, using the following categories: infants <1 year of age, children between ages of 1-4 years and children >4 years of age. Annual trends in CBSI rates overall, *Candida* CLABSI rates, and CBSI rates by age group during the study period were evaluated using Poisson regression models. The secondary outcomes of breakthrough-CBSI and mortality were evaluated using multivariable logistic regression models. Odds ratios for relevant risk factors were first calculated using univariate analysis and adjusted subsequently in multivariable models for age, gender and other confounders. Risk factors in multivariable models were considered significant at a P value of <0.05. Analyses were conducted using SPSS version 26.0 (IBM, Armonk, New York).

3. Results

3.1. Characteristics of CBSI episodes

Between 2006-2016, there were 208 episodes of CBSI in 182 patients with an incidence rate of 1.97 episodes per 1,000 patient-days. The mean age of patients overall was 6.8 years (Table 1). Infants <1 year of age and children between the age of 1-4 years had the highest CBSI incidence rates (1.77 and 2.58/1,000 patient-days, respectively). Approximately half of CBSI episodes occurred in immunocompetent patients while about a third occurred in immunocompromised patients, with the remainder occurring in neonates in the NICU (Table 1). The distribution of *Candida* species causing CBSI in each year is displayed in Figure 1. Overall, *Candida parapsilosis* was the predominant species (35.6%), followed by *C. albicans* (29.8%). *C. lusitaniae* (13.4%) was the third most prevalent species isolated surpassing *C. glabrata* (7.7%). Patients with *C. glabrata* BSI were significantly older than patients with *C. parapsilosis* (P=0.015) and patients with *C. lusitaniae* BSI (P=0.004) (Table 1).

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Table 1. Clinical characteristics and outcome of patients with *Candida* BSI.

	All *Candida* spp.	***C.parapsilosis***	***C.albicans***	***C.lusitaniae***	***C. glabrata***	***C. krusei***	***C. tropicalis***	**Other species**
N episodes (%)	208	74 (35.6)	62 (29.8)	28 (13.4)	16 (7.7)	11 (5.3)	11 (5.3)	6 (2.9)
N Patients	182	71	56	28	14	11	11	6
Males (%)	91 (50.0)	41 (57.7)	29 (51.8)	13 (46.4)	6 (42.9)	6 (54.4)	3 (27.3)	3 (50.0)
Age, mean [SD]	6.8 [7.9]	6.0 [7.2]	7.6 [7.4]	4.1 [7.0]	12.7 [9.7]	9.9 [7.6]	4.5 [4.5]	4.9 [5.3]
<1 year (%) 1-4 years (%) >4 years (%)	49 (23.6) 56 (26.9) 103 (49.5)	20 (27.0) 21 (28.4) 33 (44.6)	14 (22.6) 13 (21.0) 35 (56.5)	11 (39.3) 9 (32.1) 8 (28.6)	1 (6.3) 4 (25.0) 11 (68.8)	0 (0.0) 1 (9.1) 10 (90.9)	1 (9.1) 6 (54.5) 4 (36.4)	2 (33.3) 2 (33.3) 2 (33.3)
Immunocompetent	**106***	**35**	**32**	**14**	**13**	**3**	**8**	**1**
Gastrointestinal disorder	70	22	22	8	9	3	5	1
Cardiopulmonary disorder	29	10	7	5	5	0	2	1
Neurological disorder	16	8	5	2	0	0	1	0
Renal/urological disorder	10	4	2	2	1	0	1	0
Other underlying disease**	9	5	3	0	0	1	0	0
Immunocompromised	**73**	**25**	**21**	**9**	**3**	**8**	**3**	**4**
Bone marrow transplant	13	4	3	2	1	3	0	0
Solid organ transplant	10	1	5	1	1	1	0	1
Oncology	35	12	11	5	1	2	2	2
Other immunodeficiencies	15	8	2	1	0	2	1	1
NICU	**29**	**14**	**9**	**5**	**0**	**0**	**0**	**1**
Risk factors								
Neutropenia	29	5	9	4	2	4	2	3
Antibiotic exposure	129	46	40	15	10	9	6	3
Antifungal prophylaxis	36	13	7	4	4	5	0	3
Systemic steroids exposure	53	22	17	5	3	3	2	1
Central venous catheter	195	68	55	28	16	11	11	5
Parenteral nutrition	131	47	37	17	10	10	8	2
Mortality n (%)	25 (13.7)	9 (12.7)	5 (8.9)	3 (10.7)	2 (14.3)	3 (27.3)	2 (18.2)	1 (16.7)

Other species included C. guilliermondii (3), C. kefyr (1), C. famata (1) and C. membranifaciens (1). *28 patients had more than one underlying disorder; **Mitochondrial dysfunction (5), dystrophic epidermolysis bullosa (3), chromosomal disorder (1).

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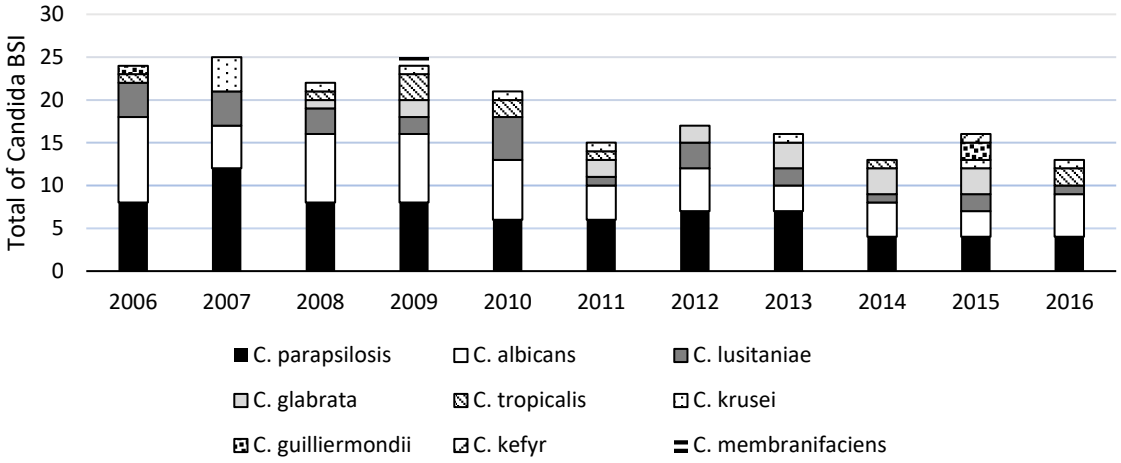

Figure 1. Number of *Candida* BSI per year, stratified by *Candida* species. Bloodstream infection episodes were tallied for each species and graphed for each year.

Thirteen patients (7.1%) had 22 episodes of recurrent CBSI (Table 2). The subsequent episodes were caused by the same species in eight instances and by a different species in fourteen. All episodes of recurrent CBSI occurred in medically complex patients with CVCs, receiving chronic parenteral nutrition. The predominant species in recurrent CBSI were *C.albicans*, *C. parapsilosis* and *C. glabrata.*

Table 2. *Candida* species distribution in 13 patients with recurrent CBSI and antifungals received in previous episodes.

	First episode	Recurrent episodes	Antifungals received in previous episodes		
			Amphotericin B	Micafungin	Fluconazole
C. parapsilosis	4	6	3		1
C. albicans	5	8	6	2	1
C. lusitaniae	3	1	1	1	
C. glabrata		6		6	
C. krusei		1	1	2	1
C. tropicalis	1				

3.2. Antifungal susceptibility

Susceptibility testing was performed for Amphotericin B (AmB) in 115 isolates, for caspofungin and voriconazole in 114 isolates, for micafungin in 89 isolates, and for fluconazole in 112 isolates (Table 3). All tested isolates were susceptible to AmB and voriconazole. Micafungin and caspofungin showed excellent activity against most *Candida* species, including all *C. parapsilosis* isolates. Almost all *Candida* species isolates were susceptible to fluconazole (96.7%). Micafungin resistance was noted in two *C. glabrata* isolates, in a patient with prior episodes of CBSI treated with micafungin (Table 4). Multi-resistance was not found in any of the tested isolates.

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Table 3. In vitro susceptibilities of *Candida* BSI.

Species	Drug	MIC (mg/L)			ECV	Susceptibility		
		MIC Range	MIC_{50}	MIC_{90}	(mg/L)[a]	S	I/SDD	R
C. albicans (31)	AMB	0.25-1	0.5	0.5	1	31	-	-
	CAS	0.016-0.5	0.031	0.125	0.25	30	1	-
	MCF	≤0.008-0.03	≤0.008	0.016	0.06	22	-	-
	FZ	0.12-1	0.25	0.5	1	31	-	-
	VOR	≤0.008-0.03	≤0.008	0.016	0.016	31	-	-
C. parapsilosis (45)	AMB	0.25-1	0.5	0.5	1	45	-	-
	CAS	0.125-1	0.25	0.5	2	44	-	-
	MCF	0.25-2	1	1	4	32	-	-
	FZ	0.25-8	1	2	2	41	3	1
	VOR	≤0.008-0.06	≤0.016	0.03	0.016	44	-	-
C. glabrata (11)	AMB	0.5-1	0.5	1	1	11	-	-
	CAS	0.016-1	0.06	0.25	0.25	9	1	1
	MCF	≤0.008 – 0.016	0.016	0.25	0.03	9	-	2
	FZ	2-64	4	16	64	10	-	1
	VOR	0.016-1	0.06	0.5	2	11	-	-
C. krusei (7)	AMB	0.5-1	1	1	128	6	-	-
	CAS	0.125-0.25	0.25	0.25	1	7	-	-
	MCF	0.06-0.125	0.06	0.125	0.25	5	-	-
	VOR	0.06-0.5	0.25	0.25	0.25	7	-	-
C. tropicalis (6)	AMB	0.25-1	0.5	1	1	6	-	-
	CAS	0.016-0.06	0.03	0.06	0.25	6	-	-
	MCF	0.016-0.03	0.03	0.03	0.06	4	-	-
	FZ	0.5-2	1	1	2	6	-	-
	VOR	0.03-0.125	0.06	0.125	0.5	6	-	-
Other spp[b] (22)	AMB	0.125-1	0.25	0.5	NA	16	-	-
	CAS	0.016-1	0.25	1	NA	22	-	-
	MCF	0.03-1	0.06	0.125	NA	16	-	-
	FZ	0.25 - 32	1	4	NA	20	-	2

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	VOR	≤0.008-0.125	0.016	0.125	NA	22	-	-
All spp. (122)	AMB	0.125-1	0.5	1,0	NA	115	-	-
	CAS	0.016-1	0.25	0.5	NA	121	1	1
	MCF	≤0.008-2	0.06	1	NA	89	-	2
	FZ	0.12-64	1	4	NA	115	3	4
	VOR	≤0.008-0.125	0.016	0.12	NA	121	-	-

AMB, amphotericin B; CAS, caspofungin; MCF, micafungin; FZ, fluconazole; VOR, voriconazole; NWT: non wild type, S: susceptible, SDD: susceptible dose dependent, I: intermediate, R: resistant; [a]ECVs: epidemiological cutoff values for 97.5% of the population, based on MICs obtained by SYO; [b]Other species include *C. lusitaniae* (19); *C. guilliermondii* (2) and *C. famata* (1).

Table 4. Clinical characteristics and minimum inhibitory concentrations (MIC) of patients with resistant species during the study period.

No.	yr	Age	CBSI species	Underlying condition	Antifungal prophylaxis	Antibiotics exposure	Fluconazole	Caspofungin	Micafungin
							MIC (mg/L)		
1	2006	3 yr	*C. parapsilosis*	Short bowel syndrome, TPN	no	yes	**8**	1	-
2	2007	3 yr	*C. albicans*	Heart transplant	no	yes	≤0.12	**0.5**	-
3	2007	5 mo	*C. lusitaniae*	Short bowel syndrome, TPN	no	no	**32**	0.5	-
5	2013	8 yr	*C. glabrata*	Intestinal failure, megabladder, TPN	no	no	2	0.25	**0.25**
6	2014	9 yr	*C. glabrata*	Intestinal failure, megabladder, TPN	Amphotericin B	no	4	**0.5**	**1**
7	2014	21 yr	*C. glabrata*	Cystic fibrosis, lung transplant	Voriconazole	yes	**64**	0.03	0.016
8	2015	7 yr	*C. lusitaniae*	Cystic fibrosis	no	yes	**16**	0.12	0.06

Yr: years, mo: months; TPN: total parenteral nutrition; Numbers 5 and 6 correspond to the same patient. In bold, resistant strains. For the C. *albicans* strain, in bold, intermediate susceptibility.

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3.3. Trends in prescription of antifungal therapy

Overall, liposomal AmB was the most frequently prescribed antifungal agent, used particularly in neonates and empirically in neutropenic patients until central nervous system involvement was excluded; micafungin use increased significantly between the first and second half of the study period (Supplementary Fig. 1). Among neonates at our center treated for CBSI in the study period, only one patient received AmB deoxycholate for 5 days of a 28-day treatment course in the first studied year, 2006. All other AmB was administered as the liposomal formulation (amBisome) in this period.

3.4. Trends in incidence of CBSI

During the study period, there was a 16% decrease per year in annual incidence rate of CBSI (incidence rate ratio (IRR): 0.84, 95% confidence interval (CI) 0.81-0.88, *P*<0.001) (Figure 2). Infants <1 year of age and children between the age of 1-4 years had the highest CBSI incidence rates overall (1.77 and 2.58/1,000 patient-days respectively). Analysis of age-specific trends in CBSI demonstrated decline in infants aged <1 year (IRR 0.78, 95% CI 0.71-0.85, *P*<0.001) and children aged 1-4 years (IRR 0.87, 95% CI 0.80-0.95, *P*=0.002). There was no decline in annual incidence of CBSI in patients older than 4 years (IRR 1.00, 95% CI 0.94-1.06, *P*=0.96) (Figure 2). Similarly, there was no decline in annual incidence of *Candida* CLABSI between 2011-2016 (IRR 0.87, 95% CI: 0.70-1.09, *P*=0.22).

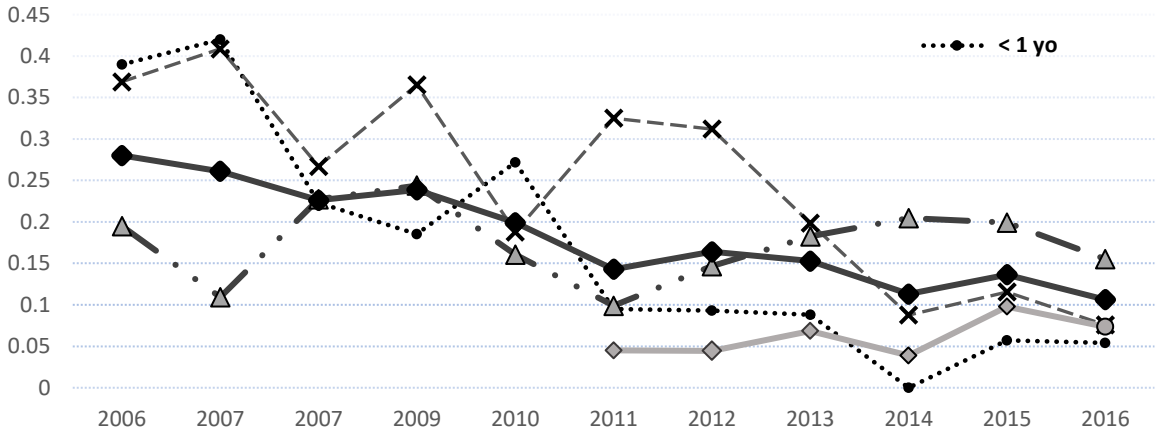

Figure 2. Annual Candida bloodstream infection rates. Overall annual CBSI rates (Cases of CBSI/1000 patient days), by age group (2006-2016) and rate of *Candida* CLABSI (CLABSI/1000 line days) from 2011 to 2016. Incidence rate ratio (IRR) of Total Candida BSI: 0.84 (95% CI: 0.81-0.88), p<0.001; IRR of Candida BSI for <1yo: 0.78 (95% CI 0.71-0.85), p<0.001; IRR of Candida BSI for 1-4yo: 0.87 (95% CI: 0.80-0.95), p=0.002; IRR of Candida BSI for >4yo: 1.00 (95% CI 0.94-1.06), p=0.96. IRR of *Candida* CLABSI: 0.87 (95% CI: 0.70-1.09), p=0.22.

3.5. Risk factors for breakthrough CBSI

BT-CBSI accounted for 17% of the CBSI (36 cases, 4 of them recurrent episodes) and did not increase over the study period. The most common infecting species in BT-CBSI was *C. parapsilosis*, followed (36%) by *C. albicans* (19.4%), *C. krusei* (14%) and *C. glabrata* (11%). Antifungal agents administered at time of BT-CBSI and species isolated are shown in Supplementary Fig. 2. Once BT-CBSI was suspected, combination therapy was chosen in 12 cases, AmB in 21 cases, and micafungin in 3 cases. All isolates were susceptible to prior prophylactic antifungals as well as empiric antifungal agents chosen. Risk factors significantly associated with BT-CBSI included underlying immunosuppression and exposure to broad-spectrum antibiotics (Table 5).

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Table 5. Risk Factors associated with breakthrough Candida blood stream infections.

Risk Factors	Odds Ratio [95% CI]	Adjusted odds ratio [95% CI]
Candida species		
Non-albican Species	1.95 [0.80-4.72]	2.15 [0.82–5.69]
C. albicans	--	Ref
Immune status		
Immunocompromised	5.64 [2.35-13.5]	3.20 [1.02-10.01]**
Neonate	2.55 [0.77-8.50]	3.54 [0.89-14.11]
Immunocompetent	--	Ref
Neutropenia		
Yes	5.51 [2.35-12.9]	2.21 [0.73-6.67]
No	--	Ref
Previous steroids		
Yes	3.38 [1.60-7.16]	1.34 [0.53–3.38]
No	--	Ref
Previous antibiotics		
Yes	6.19 [2.10-18.3]	4.83 [1.54-15.20]***
No	--	Ref
Parenteral nutrition		
Yes	1.22 [0.57-2.59]	2.07 [0.82-5.21]
No	--	Ref
Central line access		
Yes	2.63 [0.33-20.9]	0.81 [0.08-7.89]
No	--	Ref

Multivariable models adjusted for age and gender. **p<0.05, ***p<0.01.

3.6. Risk factors for mortality

Annual mortality due to CBSI did not change during the study period. The overall 30-day mortality rate was 13.7% with a median time-to-death of 6 days (range, 1-60) from onset of CBSI. Among patients who expired, eleven were immunocompromised, 7 were immunocompetent and 7 were neonates. All neonatal deaths attributed to CBSI were prior to 2012, three of which occurred in extremely preterm infants. Risk factors independently associated with death included exposure to systemic steroids and BT-CBSI (Table 6).

Table 6. Risk factors associated with death.

Risk Factors	**Odds Ratio [95% CI]**	**Adjusted odds ratio [95% CI]**
Candida species		
Nonalbican Species	1.82 [0.65-5.10]	1.85 [0.61-5.62]
C. albicans	--	Ref
[+] Immune status		
Immunocompromised	2.55 [0.94-6.93]	1.01 [0.23-4.41]
Immunocompetent	--	Ref
Neutropenia		
Yes	1.73 [0.59-5.05]	0.67 [0.21-2.20]
No	--	Ref
Breakthrough Candidemia		
Yes	4.93 [2.02-12.1]	3.60 [1.35-9.57]**
No	--	Ref
Previous Steriods		
Yes	4.82 [2.03-11.5]	3.83 [1.49-9.83]***
No	--	Ref
Gender		
Male	.47 [0.20-1.13]	0.43 [0.17-1.11]
Female	--	Ref

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Age	--	1.04 [0.99-1.10]

**p<0.05; ***p<0.01.

4. Discussion

A number of pediatric studies have addressed specific aspects of the epidemiology, species distribution, antifungal susceptibility profiles and treatment of CBSI as well as outcome-associated factors (2, 4, 9, 12-15). In our study, we reviewed these issues together from the neonatal period until young adulthood over more than a decade, providing an integrated view of trends in this infection.

The overall incidence rate of CBSI at this institution decreased by 62% over the 11-year period, consistent with similar trends reported by others (16-19). The downward trend in CBSI predominated in younger children. Cleveland et al. have also reported a decline in the crude incidence rate of CBSI in infants aged <1 year in the past 2 decades (8).

Antifungal prophylaxis cannot explain the decline in incidence since routine antifungal prophylaxis in this pediatric hospital was limited to patients with cancer. We speculate that the observed CBSI decrease is multifactorial and includes a temporal trend of improving management of underlying diseases in surgery, oncology and neonatology, as well as antimicrobial stewardship efforts. Since a *Candida* source is typically endogenous and may be less impacted by some infection control measures (e.g. healthcare worker hand hygiene or isolation precautions), preserving a balanced microbiome by reducing broad-spectrum antibiotic exposure whenever possible will likely favorably impact CBSI risk.

Recent studies showed significant decreases in overall and *Candida*-specific CLABSI (20-23). In our series, the rate of *Candida* CLABSI did not decrease in the observed half-decade for which CVC data were available, though the small annual sample sizes limit further conclusions. Measures to improve CVC care may affect *Candida* CLABSI less than those caused by skin flora, given that they frequently arise from gastrointestinal translocation (18); alternatively, achievable effects of rigorous catheter care and infection prevention may already have been maximized at the beginning of this half-decade. We like others did not find predominance of immunocompromised patients in CBSI (4, 13). However, a large majority of patients had chronic diseases and CVC.

Like others we found that non-*albicans Candida* species, particularly *C. parapsilosis*, now predominate in pediatric BSI (4, 12, 13, 24, 25). Distinct host characteristics, less use of azole prophylaxis, and preferential administration of AmB over fluconazole to treat childhood CBSI may explain the discrepancy in *Candida* species between adult and pediatric series (26). Liposomal AmB is tolerated in children much better than in adults, and its frequent use in our population may have limited emergence of antifungal-resistant species and strains given the fitness defects of amphotericin-resistant *Candida* (27).

Of note, *C. lusitaniae* was the third most common *Candida* species causing BSI in our institution. This species has rarely been reported previously as a cause of BSI and accounts for 1-2% of all non-*albicans Candida* BSI across multiple studies (4, 12, 13, 15, 24, 26, 28-30). Use of polyenes has been associated with the selection of this species (31) which can develop resistance to AmB during therapy; AmB monotherapy has been associated with poor response especially in immunocompromised patients (30, 32). In our series, all tested *C. lusitaniae* were susceptible to AmB but susceptibilities were not performed in 32% of isolates. *C. lusitaniae* has also been reported to be resistant to fluconazole, as two of our cases were. Therefore, antifungal susceptibilities of *C. lusitaniae* isolates should be routinely tested, and recalcitrant infections should be re-examined for the development of resistance.

Antifungal resistance rates were extremely low in our study, with no signs of resistance emergence over the 11-year period, possibly related to infrequent use of azole prophylaxis among our patients. Micafungin showed excellent activity against almost all *Candida* isolates including *C. parapsilosis*. Similar to other studies (33), we found all *C. parapsilosis* isolates to be susceptible to micafungin and its use was not associated with clinical failure.

In children, mortality rates associated with CBSI have been reported between 9.3% and 37% (2-4, 12, 14, 24). Heterogeneity among studies, centers and patient populations may explain the wide range of mortality in the literature. Mortality due to CBSI may be difficult to differentiate from that

caused by the underlying illness even with propensity score analysis (2, 34, 35). Consistent with other reports (28, 36), mortality in our institution did not improve over the 11-year period and was not related to antifungal resistance.

However, since 2012 CBSI-related mortality did not occur in children ≤4 years in our study. A low threshold for empiric AmB use in infants in our institution may have accounted for the improved prognosis in younger patients. AmB resistance in most *Candida* species is extremely rare despite 5 decades of use. Moreover, strains that evolve AmB resistance exhibit diminished fitness and are less virulent (27).

Notably, our experience differs from the findings of Ascher et al. (37) that lipid AmB formulations are associated with a higher mortality than the deoxycholate formulation in neonates. In that study no distinction was made between 3 available lipid formulations of AmB, while in our hospital, only liposomal AmB (Ambisome) is used. Use of different liposomal amphotericin formulations between the neonatology centers included in the Ascher study, in addition to specific center characteristics such as prevalence of extreme prematurity, also may have influenced observed mortality. Our findings support the use of liposomal AmB in neonates.

Our study has several important limitations. As a retrospective study from a single quaternary care pediatric hospital, the results may not be generalizable to children receiving care in other settings. Residual confounding from unmeasured factors, including severity of illness, is likely present and may influence associations between CBSI and mortality.

In summary, we found a decreasing incidence rate of CBSI over time. *C. parapsilosis* and *C. albicans* BSI decreased, and CBSI-related mortality was absent after 2011 in younger children, resulting in an increased median age for CBSI and fatal cases over the 11-year period. Antifungal resistance was very low and did not increase over time. Microbiologic trends in pediatric CBSI differ from those in adults possibly because AmB use is rarely limited by toxicities in children. Further decreasing CBSI and improving their outcomes may require further improvements in management of underlying comorbidities including prematurity and malignancies and improved diagnostics that permit treatment earlier in the infection course.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: Antifungal agents used for specific Candida species and Figure S2: Antifungals received at the time of breakthrough CBSI and species causing breakthrough.

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