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ORIGINAL ARTICLE

Risk factors for candidemia mortality in hospitalized children☆

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KEYWORDS
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Abstract
Objective: To evaluate risk factors associated with death due to bloodstream infection caused by *Candida* spp. in pediatric patients and evaluate the resistance to the main anti-fungal used in clinical practice.
Methods: This is a cross-sectional, observational, analytical study with retrospective collection that included 65 hospitalized pediatric patients with bloodstream infection by *Candida* spp. A univariate analysis was performed to estimate the association between the characteristics of the candidemia patients and death.
Results: The incidence of candidemia was 0.23 cases per 1000 patients/day, with a mortality rate of 32% ($n = 21$). Clinical outcomes such as sepsis and septic shock ($p = 0.001$), comorbidities such as acute renal insufficiency ($p = 0.01$), and risks such as mechanical ventilation ($p = 0.02$) and dialysis ($p = 0.03$) are associated with increased mortality in pediatric patients. The resistance and dose-dependent susceptibility rates against fluconazole were 4.2% and 2.1%, respectively. No resistance to amphotericin B and echinocandin was identified.
Conclusion: Data from this study suggest that sepsis and septic shock, acute renal insufficiency, and risks like mechanical ventilation and dialysis are associated with increased mortality in pediatric patients. The mortality among patients with candidemia is high, and there is no species

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difference in mortality rates. Regarding the resistance rates, it is important to emphasize the presence of low resistance in this series.

PALAVRAS-CHAVE
Candidemia;
Mortalidade pediátrica;
Infecção da corrente sanguínea;
Hemocultura

Fatores de risco de mortalidade por candidemia em crianças internadas

Resumo
Objetivo: Avaliar os fatores de risco associados ao óbito por infecção da corrente sanguínea causada pela *Candida* spp em pacientes pediátricos e avaliar a resistência ao principal antifúngico usado na prática clínica.
Métodos: Este é um estudo transversal, observacional e analítico com coleta retrospectiva que incluiu 65 pacientes pediátricos internados com infecção da corrente sanguínea por *Candida* spp. Foi realizada uma análise univariada para estimar a associação entre as características dos pacientes com candidemia e o óbito.
Resultados: A incidência de candidemia foi de 0,23 casos em cada 1000 pacientes/dia, com taxa de mortalidade de 32% (n = 21). O resultado clínico como sepse e choque séptico (p = 0,001), comorbidades como insuficiência renal aguda (p = 0,01) e riscos como ventilação mecânica (p = 0,02) e diálise (p = 0,03) estão associados ao aumento da mortalidade em pacientes pediátricos. As taxas de resistência e susceptibilidade dose-dependente contra o fluconazol foram de 4,2% e 2,1%, respectivamente. Não foi identificada nenhuma resistência à anfotericina B e equinocandina.
Conclusão: Os dados de nosso estudo sugerem que a sepse e choque séptico, insuficiência renal aguda e riscos como ventilação mecânica e diálise estão associados ao aumento da mortalidade em pacientes pediátricos. A mortalidade entre pacientes com candidemia é alta, e não há nenhuma diferença nas taxas de mortalidade entre as espécies. Sobre a resistência, é importante enfatizar a presença de baixa resistência nesta série.

Introduction

Infection by *Candida* spp. is a significant cause of morbidity and mortality among hospitalized children, with a mortality rate ranging from 10% to 47%[1,2] Current changes in the prevalence of *Candida* spp. in Latin America and Brazil have transitioned from *Candida albicans* to non-*C. albicans*.[3,4]

A recent laboratory surveillance study presented the epidemiology of candidemia in Latin America. This report draws attention to the high percentage of candidemia episodes among children (approximately 45%), in contrast with a patient series published in Europe and the United States.[5]

Most studies of risk factors for mortality in patients with candidemia have focused on adult populations. However, risk factors for mortality identified in adults may not be relevant in pediatric patients, and studies defining these risks and resistance data in the pediatric population are also limited.[1,5]

The objective of this study was to evaluate risk factors associated with death due to bloodstream infection caused by *Candida* spp. in pediatric patients and evaluate the resistance to the main anti-fungal used in clinical practice.

Methods

Study setting

This is a series of cases of pediatric patients with positive blood culture for *Candida* spp. conducted in a tertiary care children's hospital with 400 beds. Data from patients with ages ranging from 0 to 18 years who presented with candidemia were verified as positive blood cultures for *Candida* in samples collected from peripheral vein or vascular catheter. The studied included patients hospitalized from September 2008 up to September 2011.

Study design and fungal samples

This is a cross-sectional, observational, analytical study with retrospective collection. The demographic data and clinical characteristics such as catheter use, medication use prior to candidemia, and associated comorbidities (prematurity, cancer, human immunodeficiency virus infection, heart disease, lung disease, neurological disease, transplantation, acute and chronic renal insufficiency, mucositis, and neutropenia) were analyzed.

In addition, to evaluate the presence of associated bacteremia (before and after candidemia) and persistent candidemia, potential risks such as use of mechanical ventilation, total parenteral nutrition, use of central venous catheter, and dialysis were also considered. The data were used to assess the relative mortality risk, and the antifungal treatment and its effects.

The severity of illness at the time of candidemia has also been reported as a risk factor for mortality. The patients were evaluated for the presence of fever, hypotension, and/or septic shock signs (hypothermia or hyperthermia, altered mental status, and peripheral vasodilation or vasoconstriction) in accordance with criteria established in 2009 by Brieley et al.[6]

All samples were collected before the administration of antifungal drugs to patients presenting fever and suspected of fungemia, who underwent antibiotic therapy, and had a prolonged hospital stay.

Microbiology studies

Blood cultures of all 65 cases were performed using a BD BACTEC 9120 Blood Culture System (Becton Dickinson, Franklin Lakes, USA). The Vitek-2 system (bioMérieux, Durham, USA) was used for species identification. Susceptibility tests to antifungals were performed in 47 samples. Tests for amphotericin B (Sigma–Aldrich Quimica, Madri, Spain), fluconazole (Pfizer, Madrid, Spain), micafungin (Mycamine®; Astellas Pharma Inc., Toyama, Japan), and anidulafungin (Ecalta-Pfizer, Kent, United Kingdom) were performed using the broth microdilution method according to the M27-S4 protocols (2012) of the Clinical and Laboratory Standards Institute.[7]

Statistical analysis

A univariate analysis was performed to determine the association between the characteristics of the candidemia patients and death. Categorical variables were compared by using Fisher's exact test or the chi-squared test, with a significance level of $p < 0.05$. Statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria).

Due to the complexity of the combinations and the small number of cases for some categories, the analysis of the variable ''prior pathological condition'' was performed by using patient groups with at least one of the following conditions: prematurity, positive human immunodeficiency virus (HIV), heart failure, pulmonary disease, neurological disease, transplantation, acute and chronic renal insufficiency, mucositis, and/or cancer, for a comparison with the patients with other isolated or associated pathological conditions. The same approach was used for the analysis of potential risk factors (neutropenia, parenteral nutrition, mechanical ventilation, and/or dialysis).

The study was approved by the Institutional Review Board of the Hospital.

Table 1 Species distribution of 65 episodes of candidemia identified by Vitek-2.

Species	Number of isolates	Percentage
C. albicans	24	37%
C. parapsilosis	20	31%
C. tropicalis	5	8%
C. guilliermondii	3	5%
C. haemulonii	3	5%
C. krusei	2	3%
C. glabrata	2	3%
Others[a]	6	12%

[a] Other species – *C. lusitaniae* (1), *C. pelliculosa* (1); *C. intermedia* (1), *C. famata* (1), *C. norvegiensis* (1); *C. lipolytica* (1).

Results

The study included 65 patients with candidemia, in accordance with the aforementioned inclusion criteria. The mean age was 3.3 years (SD ± 1.8) and median, 1.5 years (range, 0–15.7 years). Thirty-eight episodes (58.5%) of candidemia occurred in children younger than 2 years, including eight newborns, and 27 episodes (41.5%) occurred in children older than 2 years old, which include ten (15.4%) in preschool age. Thirty-seven (57%) of the patients were male and 28 (43%) were female. The incidence of candidemia was 0.23 cases per 1000 patients/day and 0.9 cases per 1000 admissions, with a mortality rate of 32% ($n = 21$).

A microbiological summary of the *Candida* spp. isolated is presented in Table 1. Only one *Candida* spp. was isolated from each case, except one case of mixed *Candida* spp. and bacteria-positive blood cultures.

Upon consideration of the clinical symptoms at the time of candidemia, patients who presented with sepsis or septic shock had an increased mortality rate, whereas the patients who only presented fever had a lower mortality rate ($p = 0.001$).

Regarding pathological conditions prior to candidemia, it was noted that patients with acute renal insufficiency, whether or not in combination with other pathological conditions, were associated with increased mortality ($p = 0.01$).

Risk factors like mechanical ventilation ($p = 0.03$) and dialysis ($p = 0.02$), whether or not in combination with other factors, were associated with increased mortality in the analysis.

Table 2 summarizes the main demographic data and clinical characteristics of the patients associated with death or survival outcomes.

Upon consideration of the variable blood culture conducted within 30 days of candidemia, a significant p-value ($p = 0.001$) demonstrated increased mortality in the group with positive blood culture for *Candida* spp. and/or bacteria. After the initiation of antifungal treatment, control blood cultures were collected from 55 of the 65 patients with candidemia, while the remaining patients were either discharged from the hospital ($n = 3$) or died ($n = 7$) during the period of candidemia diagnosis.

Still in the univariate analysis other potential risk factors were investigated, such as the use of antibiotics and

Table 2 Demographic data, clinical characteristics, and clinical outcome in hospitalized pediatric patients with candidemia.

Variable	Number of patients			Percentage of death (%)	*p*-Value
	Survival	Death	Total (%)		
Age					0.12
<28 days (neonatal)	3	5	8 (12.3)	62.5	
28 days to 2 years	20	10	30 (46.2)	33.3	
>2 years	21	6	27 (41.5)	22.2	
Identified species					0.79
C. albicans	17	7	24 (36.9)	29.2	
Other species	27	14	41 (63.1)	34.1	
Associated bacteremia prior or during candidemia					0.52
Yes	11	3	14 (21.5)	21.4	
No	33	18	51 (78.5)	35.3	
Blood culture performed within 30 days after candidemia					**0.001**
No	3	7	10 (15.4)	70.0	
Yes, negative	**27**	2	29 (44.6)	6.9	
Yes, positive for bacteria	5	4	9 (13.8)	44.4	
Yes, positive for Candida of the same species	9	8	17 (22.1)	47.1	
Hospital unit					0.11
Non-ICU	25	7	32 (49.2)	21.8	
ICU	19	14	33 (50.8)	42.4	
Severity of illness (fever, hypotension, septic shock)					**0.001**
Other (hypotension and/or septic shock)	4	**10**	14 (21.9)	71.4	
Only fever	**28**	4	32 (50)	12.5	
None of the above	11	7	18 (28.1)	38.9	
Catheter (CVC, PICC, arterial, or totally implanted catheter)					0.78
Yes	30	13	43 (66.2)	30.2	
No	14	8	22 (33.8)	36.4	
Prior pathological conditions[a]					
Group 1					0.71
Prior pathological conditions except pulmonary disease	36	16	52 (83.9)	30.8	
At least pulmonary disease	6	4	10 (16.1)	40.0	
Group 2					0.75
Prior pathological conditions except neurological disease	33	15	48 (77.4)	31.3	
At least neurological disease	9	5	14 (22.6)	35.7	
Group 3					0.27
Prior pathological conditions except mucositis	37	15	52 (83.9)	28.8	
At least mucositis	5	5	10 (16.1)	50.0	
Group 4					**0.01**
Prior pathological conditions except acute renal insufficiency	40	14	54 (87.1)	25.9	
At least acute renal insufficiency	2	6	8 (12.9)	75.0	
Group 6					0.74
Prior pathological conditions except cancer	34	15	49 (79)	30.6	
At least cancer	8	5	13 (21)	38.5	
Potential risk factors (RF)[b]					
Group 1					0.42
Other (parenteral nutrition, mechanical ventilation, and/or dialysis)	15	11	26 (40)	42.3	

Table 2 (*Continued*)

Variable	Number of patients			Percentage of death (%)	*p*-Value
	Survival	Death	Total (%)		
None of the assessed RF	20	7	27 (41.5)	25.9	
At least[c] neutropenia	9	3	12 (18.5)	25.0	
Group 2					0.39
Other (mechanical ventilation, dialysis, and/or neutropenia)	15	6	21 (32.3)	28.6	
None of the assessed RF	20	7	27 (41.5)	25.9	
At least parenteral nutrition	9	8	17 (26.2)	47.1	
Group 3					**0.02**
Other (parenteral nutrition, dialysis, and/or neutropenia)	13	2	15 (23.1)	13.3	
None of the assessed RF	20	7	27 (41.5)	25.9	
At least mechanical ventilation	11	12	23 (35.4)	52.2	
Group 4					**0.03**
Other (parenteral nutrition, mechanical ventilation, and/or neutropenia)	23	9	32 (49.2)	28.1	
None of the assessed RF	20	7	27 (41.5)	25.9	
At least dialysis	1	5	6 (9.2)	83.3	

ICU, intensive care unit; CVC, central venous catheter; PICC, peripheral implanted central catheter.
[a] Prior pathological conditions: pulmonary disease, prematurity, cancer, human immunodeficiency virus (HIV), heart disease, neurological disease, transplantation, acute and chronic renal insufficiency, mucositis, and/or neutropenia.
[b] Potential risk factors: parenteral nutrition, mechanical ventilation, dialysis, and neutropenia.
[c] At least: the patient has at least one risk factor assessed, whether or not combined with other factors.

previous abdominal surgery, which have not been associated with increased mortality.

Similarly, due to the increase of non-*albicans* spp. in recent years, univariate analyses between the *albicans* and non-*albicans* spp. were performed and no increased mortality was observed.

Antifungigram performed on 47 *Candida* samples found a dose-dependent susceptibility to fluconazole in one strain of *C. glabrata*. One sample of isolated *C. glabrata* and *C. albicans* presented resistance to fluconazole, with a minimum inhibitory concentration (MIC) of 64 μg/mL and 32 μg/mL, respectively (Clinical and Laboratory Standards Institute, CLSI; 2012).[7] No resistance to amphotericin B and echinocandin was identified in the 47 samples tested.

Therefore, the resistance and dose-dependent susceptibility rates against fluconazole were 4.2% (2/47) and 2.1% (1/47), respectively.

In this series, the most frequently antifungal therapy used was amphotericin B deoxycholate (60.0%), followed by fluconazole (38.0%), either alone or in combination. Six patients (9.2%) received amphotericin B deoxycholate and fluconazole in combination, and five patients (7.6%) received fluconazole followed by amphotericin B deoxycholate. Liposomal amphotericin B was used in two cases and caspofungin in one case.

Discussion

Significant data were produced regarding mortality and risk factors for mortality in this series of 65 pediatric patients with invasive candidemia.

There are few works that have studied unselected pediatric populations with invasive candidiasis/candidemia in Europe and in Latin America. In 2012, Tragiannidis et al. published the first series of cases in Germany describing microbiological and clinical epidemiology.[8] Pasqualoto et al., in 2007, held the first published Brazilian study on risk factors for mortality in an unselected pediatric population.[4] The present series of 65 cases is the second Brazilian publication, to the authors' knowledge, regarding risk factors for mortality in pediatric patients with the same characteristics.

This study demonstrated that patients who presented exclusively with fever had a lower mortality rate than those with severe signs such as sepsis or septic shock with or without fever. These severe signs are *per se* considered risk factors for death. On the other hand, the presence of fever may have attracted persistent attention of the physicians in charge to look more extensively for a cause and, in these patients, allowed earlier diagnosis of candidemia, providing them with appropriate medications, leading to a better outcome.

A prior pathological condition considered as another risk factor for mortality was acute renal insufficiency, which increased patient mortality whether or not in combination with other pathological conditions. Recently, Santolaya et al. showed the same result in a series of children patients from Latin America.[9]

Upon consideration of the most frequent risk factors for acquiring candidemia, it was found that the use of mechanical ventilation and dialysis (including hemodialysis and peritoneal dialysis) were considered risk factors for mortality in *Candida* infection. Until now, all the studies that

analyzed pediatric mortality from *Candida* infection have not demonstrated the association between dialysis and mortality, as the present study has.

Hammoud et al.[10] reported that persistent candidemia was associated with an increased risk of death. In contrast, Robinson et al.[11] observed that an increase in the interval between blood culture and the beginning of antifungal therapy (>1 day) in newborns was associated with an increased incidence of persistent candidemia, though not associated with increased mortality.

The present study showed an increased mortality in the patient group with a positive blood culture within 30 days after candidemia, regardless whether the positive results were for *Candida* spp. and/or bacteria. Three patients had three positive blood cultures for *Candida*, taking on average ten days to obtain negative blood cultures. However, there was a limitation regarding the absence of catheter management information, and it is possible that this increase in mortality could be linked with catheter maintenance in the patient. Even so, it is important to highlight that that the prompt removal of lines with initiation of antifungal treatment are the cornerstones of management, in addition to performing a control blood culture every 72 h after the first *Candida*-positive result, until two negative blood cultures.[12]

Analyzing mortality and *Candida* spp. showed no difference between *albicans* and non-*albicans* spp. However, previous studies have suggested that *C. parapsilosis* is a less virulent species, and *C. parapsilosis* fungemia in adults and children is associated with lower mortality than non-*parapsilosis* candidemia.[9,13,14] It is probable that this result of no difference between species in the present study is due to lower virulence attributed *C. parapsilosis* spp., which in the present series represented 31% of isolated *Candida* spp. Differently, Santolaya et al. linked mortality with *C. albicans* in neonates and *C. tropicalis* in children.[7]

Diseases caused by species commonly resistant to azoles were extremely rare among pediatric candidemia.[15] In this series, there was only one case of dose-dependent reduced susceptibility to fluconazol and two cases with fluconazol resistance. Nevertheless, most patients (60%) were treated with amphotericin B deoxycholate and only 38% with fluconazol (alone or in combination therapy), following the orientation of institutional protocol, since a large number of patients had failed therapy with fluconazole in *Candida* sepsis cases. Echinocandins have been recently introduced as treatment in life-threatening cases (after 2012). Recently, Herkert et al.[16] showed disturbing *Candida* resistance rates to echinocandins in a university hospital, reflecting the impact of extensive use of these antifungal agents as prophylactics.

There were some potential limitations in this study. The first limitation is related to the number of patients included, since this study was conducted in one site only. Second, ideally more information regarding the candidemia diagnosis would be available. In cases where the blood was obtained through the catheter, it is impossible to know whether this represents true candidemia or catheter colonization. Besides this, it would be important to know how many patients were diagnosed by obtaining blood through the catheter, as well as the catheter management once candidemia had been diagnosed. After all, *C. parapsilosis* was the second most frequent *Candida* spp. in this series.

In conclusion, data from this study suggest that sepsis and septic shock, acute renal insufficiency, and risks like mechanical ventilation and dialysis are associated with increased mortality in pediatric patients. The mortality among patients with candidemia is high, and there is no species difference in mortality rates. The results also confirm the elevated incidence of bloodstream infections caused by *Candida* spp. other than *Candida albicans*. Regarding the resistance rates, it is important to emphasize the presence of low resistance in this series.

Conflicts of interest

The authors declare no conflicts of interest.

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