Active Surveillance of Candidemia in Children from Latin America

A Key Requirement for Improving Disease Outcome

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Background: Active surveillance is necessary for improving the management and outcomes of patients with candidemia. The aim of this study was to describe the epidemiologic and clinical features of candidemia in pediatric patients in Latin America.

Method: Prospective, multicenter, surveillance study of candidemia in a pediatric population from 23 hospitals in 8 Latin America countries between November 2008 and October 2010.

Results: Three hundred and two cases of candidemia were reported with a median incidence of 0.81/1000 admissions. Eighty nine (29%) were neonates. The main risk factors were prematurity, intensive care unit (ICU) admission, parenteral nutrition, respiratory disease and mechanical ventilation in neonates and malignancy, neutropenia, neurological disease and previous use of corticosteroids in children. The main species isolated in neonates and children were *Candida albicans* (43.8% and 35.7%), *Candida parapsilosis* (27.0% and 26.3%) and *Candida tropicalis* (14.6% and 14.6%), respectively. The most frequent antifungal therapy used in neonates and children was deoxycholate-amphotericin-B (43.8% and 29.1%) and fluconazole (28.1% and 53.1%). Seventeen neonates (19.1%) and 20 children (9.4%) did not receive antifungal therapy. The 30-day survival rate was 60% in neonates and 72% in children ($P = 0.02$). Survival was significantly higher in treated than in nontreated neonates (72% vs. 24%; $P < 0.001$). A multivariate analysis showed that independent predictors for 30-day mortality in children were renal disease (odds ratio: 4.38, 95% confidence interval: 1.92–10.1, $P < 0.001$) and receipt of corticosteroids (odds ratio: 2.08, 95% confidence interval: 1.04–4.17, $P = 0.04$).

Conclusions: To our knowledge, this is the first prospective, multicenter surveillance study of candidemia in children in Latin America. This epidemiologic information may provide us with methods to improve preventive, diagnostic and therapeutic strategies in our continent.

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Candidemia is a major cause of morbidity and mortality in hospitalized patients. Its incidence has increased during the last decade as a consequence of changes in patients demographic characteristics.[1] *Candida* spp. is the third more common pathogen isolated in pediatric bloodstream infections in the United States and Europe.[2,3]

There is limited information on the epidemiology of candidemia in pediatric populations. One retrospective study of the incidence of candidemia in the United States in 2000 reported 0.43 pediatric cases/1000 hospital admissions [95% confidence interval (CI): 0.35–0.52] compared with 0.30 adult cases/1000 hospital admissions (95% CI: 0.26–0.34).[1]

There are some differences in risk factors for candidemia between children and adults. In the pediatric population, 3 main groups of patients are affected by candidemia: premature neonates,[4–7] immunocompromised children (particularly cancer patients)[8–10] and patients admitted to an intensive care unit (ICU).[11,12] Furthermore, it has been suggested that candidemia-associated mortality in pediatric patients is generally lower than in adults, ranging from 10% to 23%, compared with 43% to 54% in adults.[1,13,14]

Data on incidence, risk factors and mortality of candidemia in the pediatric population of Latin America (LA) are scarce. There are some epidemiologic studies from Argentina, Brazil and Colombia that include children in the general analysis, but these studies do not stratify their population by age.[15–17] Surveillance is necessary for a better understanding of candidemia in neonates and children in our region; results from which may define best future practices for prevention, diagnosis and management.

The Latin America Invasive Mycosis Network was formed in 2007 with the aim to identify priorities in research and educational activities in the region. The group is made up of physicians (specialists in infectious diseases, hematology/oncology, hematopoietic stem cell transplantation and microbiology), from 8 LA countries. The aim of this prospective, multicenter study was to describe epidemiologic and clinical features of candidemia in children in LA.

PATIENTS AND METHODS

Overall Study design

A prospective, multicenter, laboratory-based observational surveillance study was conducted in 23 tertiary care hospitals in 8 LA countries (Argentina, Brazil, Chile, Colombia, Ecuador, Honduras, Mexico and Venezuela), belonging to the Latin America Invasive Mycosis network, between November 2008 and October 2010.

All pediatric patients with candidemia were eligible for inclusion in the study and were followed for 30 days from the date of the incident candidemia. An investigator in each hospital was designated to visit the microbiology laboratory on a daily basis to capture all episodes of candidemia, and trained to complete a comprehensive case report form once candidemia was diagnosed. The case report form contained detailed information about demographics, concomitant conditions, treatment with antifungal agents and outcomes. All clinical information was sent using a web-based system (SPSS, Inc., Chicago, IL). All isolates were identified at species level in the local laboratory and then sent to the Special Mycology Laboratory at Universidade Federal de São Paulo for species confirmation and antifungal susceptibility testing. The study was approved by the ethical committee of each of the hospitals involved.

Microbiologic Identification and Antifungal Susceptibility

All hospitals had automated blood culture systems (either Bactec or BacT-ALERT). Isolates were identified according to their microscopic morphology on cornmeal Tween 80 agar and complemented by biochemical tests using the ID 32C system (BioMérieux AS, Marcy 1´ Etoile, France). Antifungal susceptibility tests were performed using a broth microdilution assay following the methods recommended by the Clinical and Laboratory Standards Institute (CLSI).[18] The following antifungal drugs were tested: amphotericin B (Sigma Chemical Corporation, St Louis, MO), fluconazole, voriconazole and anidulafungin (Pfizer Incorporated, New York, NY). The assays were incubated at 35º C for 24 hours.

For amphotericin B, isolates with minimum inhibitory concentration (MIC) ≤1 μg/mL were considered susceptible and those with MIC ≥2 μg/mL were considered resistant.[19] The MIC breakpoints for fluconazole were as follows: *Candida albicans*, *Candida parapsilosis* and *Candida tropicalis* isolates with MIC ≤2 μg/mL were considered susceptible, those with MIC 4 μg/mL were considered susceptible dose-dependent (SDD) and those with MIC ≥8 μg/mL were considered resistant; *Candida glabrata* isolates with MIC ≤32 μg/mL were considered SDD, and MIC ≥64 μg/mL were considered resistant.[20] All *Candida krusei* isolates were considered resistant regardless of the MIC value. For voriconazole, isolates with MIC ≤2 μg/mL were considered susceptible, those with MIC 4 μg/mL were considered SDD and those with MIC ≥8 μg/mL were considered resistant.[18] For anidulafungin, isolates of *C. albicans*, *C. tropicalis* and *C. krusei* with MIC ≤ 0.25 μg/mL were considered susceptible, those with MIC 0.5 μg/mL were intermediate and those with MIC ≥1 μg/mL were considered resistant. For *C. parapsilosis* isolates with MIC ≤2 μg/mL were susceptible, 4 μg/mL were intermediate and ≥8 μg/mL were resistant. For *C. glabrata,* the values were as follows: ≤0.12 μg/mL susceptible, 0.25 μg/mL intermediate and ≥0.5 μg/mL resistant.[20]

Definitions

An episode of candidemia was defined by the isolation of *Candida* species from 1 or more blood cultures in a patient with clinical signs of infection. If more than 1 blood culture was positive, a new episode of candidemia was defined if more than 30 days had elapsed since the first positive blood culture (incident candidemia). Neonates were defined as patients with age ≤28 days, and children were defined as patients > 28 days and <18 years of age. Persistent candidemia was defined as any positive blood culture for *Candida* species after 72 hours of antifungal therapy. Early central venous catheter (CVC) removal was defined as removal within 48 hours from antifungal treatment initiation. Appropriate treatment was defined as start of an antifungal agent active against the bloodstream isolate within 24 hours from the date of the incident candidemia.

Statistical Analyses

Incidence density of candidemia was calculated using the number of episodes of candidemia as numerators and admissions and patient-days as denominators. Dichotomous variables were compared using Fisher or χ^2 test, as appropriate, and continuous variables were compared using the Wilcoxon test. Clinical and laboratory variables associated with death in both neonates and children were identified by univariate analysis comparing data from surviving patients with those who died. Variables with $P < 0.05$ by univariate analysis were incorporated in a multivariate analysis, calculating the odds ratio (OR) with the corresponding 95% CI. All statistical analyses were performed in the SPSS software (version 15, SPSS, Inc.). $P < 0.05$ were considered statistically significant.

RESULTS

Population Characteristics

During the 24-month study period, we evaluated 302 consecutive cases of candidemia in patients <18 years of age. Of these 302 episodes of candidemia, 89 (29%) occurred in neonates (≤28 days) and 213 (71%) in children. The median age at candidemia presentation was 16 days (range 1–28 days) in neonates and 2 years (range 0.2–17 years) in children. Male subjects made up 46% of the neonates and 65% of the children. The median number of days of hospitalization before diagnosis of candidemia was 12 days (range 0–28) and 14.5 days (range 0–176) in neonates and children, respectively. Incidence of candidemia was calculated

Table 1. Age-specific Concomitant Conditions in 302 Neonates and Children With Candidemia

	Neonates N (%) N = 89	Children N (%) N = 213	*P* value
Prematurity (<37 weeks)	47 (52.8)	8 (3.8)	<0.001
Admission to an ICU	70 (79)	72 (33.8)	<0.001
Malignancy	0	54 (25.4)	<0.001
Neutropenia (< 500 cells/mm^3)	1 (1.1)	38 (17.8)	<0.001
Solid or HSCT	0	2 (0.9)	1.00
Central venous catheter	63 (70.8)	133 (62.4)	0.17
Parenteral nutrition	43 (48.3)	44 (20.7)	<0.001
Cardiovascular disease	18 (20.2)	30 (14.1)	0.18
Neurological disease	6 (6.7)	39 (18.3)	0.01
Respiratory disease	27 (30.3)	34 (16.0)	0.005
Mechanical ventilation	60 (67.4)	64 (30.0)	<0.001
Renal disease	10 (11.2)	32 (15.0)	0.39
Liver disease	2 (2.2)	14 (6.6)	0.16
Recent surgery	26 (29.2)	85 (39.9)	0.08
Abdominal surgery	18 (20.2)	46 (21.6)	0.79
Burns	0	7 (3.3)	0.11
Previous receipt of corticosteroids	12 (13.5)	68 (31.9)	0.001
Previous receipt of antibiotics	85 (95.5)	204 (95.8)	1.00
Previous receipt of fluconazole	15 (16.9)	25 (11.7)	0.23

HSCT, hematopoietic stem cell transplant; ICU, intensive care unit.

only in the pediatric hospitals, on base of 116,298 hospital admissions, 550,140 patients-day and 94 episodes of candidemia, with a median incidence of 0.81/1000 admissions (range 0.47–1.64) and 0.17/1000 patient-days (range 0.16–0.25).

Concomitant Conditions in Neonates and Children With Candidemia

Table 1 shows a comparison between the main concomitant conditions seen in neonates and children. Most of the neonates were premature (52.8%). Hospitalization in an ICU (79%), use of parenteral nutrition (48.3%), respiratory disease (30.3%) and mechanical ventilation (67.4%) were significantly more frequent in neonates ($P < 0.05$). Children were more likely to have malignancy (25.4%), neutropenia (17.8%), neurological disease (18.3%) and previous use of corticosteroids (31.9%). The proportion of other factors, such as central venous catheter (70.8% vs. 62.4%, $P = 0.17$) and previous antibacterial therapy (95.5% vs. 95.8%, $P = 1.0$) was similar in both groups.

Microbiologic Results

The main species isolated in neonates and children were *C. albicans* (43.8% and 35.7%), *C. parapsilosis* (27% and 26.3%), *C. tropicalis* (14.6% and 14.6%) and *Candida guilliermondii* (4.5% and 12.7%), the *Candida guilliermondii* significantly less frequent in neonates compared with children ($P = 0.03$). Conversely, *C. glabrata* was infrequent in both group (3.4% and 3.3%; Table 2). There was some variability in species distribution in the different countries. *C. albicans* was the most frequent species in Argentina (62.2%), Brazil (33.8%), Colombia (41.9%) and Ecuador (51.4%); Chile and Venezuela had a higher proportion of *C. parapsilosis* (47.4% and 47.2%, respectively) and Honduras had similar proportions of *C. albicans* (28.9%), *C. tropicalis* (22.7%) and *C. guilliermondii* (22.7%). The higher proportion of *C. parapsilosis* in Venezuela could be due to the high proportion of neonates (69.2%), that was not the situation in Chile, since only 15.8% of patients were neonates.

All isolates of *C. albicans*, *C. parapsilosis* and *C. tropicalis* (N = 239) were susceptible to fluconazole, with the exception of 1 *C. parapsilosis* isolate, which was SDD. Of 10 isolates of *C. glabrata*, 9 were SDD and 1 was resistant. For anidulafungin, there was 1 *C. tropicalis* isolate (2.3%) with intermediate susceptibility.

Treatment

The most commonly used antifungal therapies in neonates and children were deoxycholate-amphotericin-B (43.8% and 29.1%) and fluconazole (28.1% and 53.1%; Table 3). An echinocandin was used in 4.5% and 3.8% of neonates and children, respectively. Seventeen neonates (19.1%) and 20 children (9.4%) did not receive antifungal therapy.

TABLE 2. Species Distribution of 302 Episodes of Candidemia in Neonates and Children, by Age

	Neonates N (%) N = 89	Children N (%) N = 213	Overall N = 302
C. albicans	39 (43.8)	76 (35.7)	115 (38.1)
C. parapsilosis	24 (27.0)	56 (26.3)	80 (26.5)
C. tropicalis	13 (14.6)	31 (14.6)	44 (14.6)
C. guilliermondii	4 (4.5)*	27 (12.7)*	31 (10.3)
C. glabrata	3 (3.4)	7 (3.3)	10 (3.3)
C. krusei	4 (4.5)	5 (2.3)	9 (3.0)
Other†	2 (2.2)	11 (5.1)	13 (4.2)

* P value nonsignificant for all species, except for *C. guilliermondii* ($P = 0.03$).

† Other *Candida* species: Neonates—*C. lusitaniae* (1), *C. intermedia* (1).

Children—*C. haemulonii* (3), *C. pelliculosa* (3), *C. intermedia* (2), *C. norvegiensis* (1), *C. lusitaniae* (1), *C. albicans* + *C. glabrata* (1).

TABLE 3. Primary Antifungal Therapy in 302 Neonates and Children, by Age

Primary treatment*	Neonates N (%) N = 89	Children N (%) N = 213	P value
d-AMB	39 (43.8)	62 (29.1)	0.01
Fluconazole	25 (28.1)	113 (53.1)	<0.001
l-AMB	1 (1.1)	4 (1.9)	1.00
Echinocandin	4 (4.5)	8 (3.8)	0.75
Voriconazole	2 (2.3)	2 (0.9)	0.58
No treatment	17 (19.1)	20 (9.4)	0.02

* Primary treatment unknown in 5 patients (1 neonate and 4 children).

d-AMB, deoxycholate-amphotericin B; l-AMB, Lipid formulation of amphotericin B.

Outcomes

The 30-day survival was 60% in neonates and 72% in children ($P = 0.02$). Survival was significantly higher in treated versus nontreated neonates (72% vs. 24%, $P < 0.001$) but not significantly higher in treated versus nontreated children (77% vs. 58%, $P = 0.09$). An analysis of the 17 neonates who did not receive treatment showed that 14 (82.4%) died within 3 days of the incident candidemia and 11 (64.7%) presented with hypotension and received vasoactive drugs.

Variables evaluated as predictors of 30-day mortality were prematurity, admission to an ICU, malignancy, neutropenia, cardiovascular, respiratory, neurological, renal and liver disease, receipt of parenteral nutrition, mechanical ventilation, corticosteroids, antibiotics, recent surgery, *Candida* species, persistent candidemia, early CVC removal, receipt of treatment and use of appropriate treatment. In neonates, in addition to not receipt of treatment, *C. albicans* candidemia was the only variable associated with higher mortality rate (51.3% vs. 26.0% for other species, $P = 0.045$). If we exclude from the analysis patients who did not receive treatment, no other variable was significant. For children, predictors of 30-day mortality by univariate analysis were neutropenia ($P = 0.02$), mechanical ventilation ($P = 0.03$), renal disease ($P < 0.001$), liver disease ($P = 0.04$), receipt of corticosteroids ($P = 0.01$) and candidemia due to *C. tropicalis* ($P = 0.04$), whereas candidemia due to *C. parapsilosis* was protective ($P = 0.04$). Neither persistent candidemia nor early CVC removal was associated with outcome in both, neonates and children. By multivariate analysis, independent predictors for 30-day mortality in children were renal disease (OR: 4.38, 95% CI: 1.92–10.10, $P < 0.001$) and receipt of corticosteroids (OR: 2.08, 95% CI: 1.04–4.17, $P = 0.04$), with a protective effect of candidemia due to *C. parapsilosis* (OR: 0.35, 95% CI: 0.15–0.85, $P = 0.02$).

DISCUSSION

To our knowledge, this is the first prospective, multicenter surveillance study of candidemia in a pediatric population in LA. A number of previous worldwide studies have analyzed factors that influence the incidence of candidemia in children; however, few have compared age-specific concomitant conditions in the same cohort. One prospective study by Blyth *et al*. reported 1005 cases of candidemia in Australia, including 33 neonates, 110 children and 862 adults.[21] Prematurity and ICU admission were the main risk factors in neonates, while hematologic malignancy and neutropenia were more frequent in children. Another study, from Zaoutis *et al*[12] reported risk factors and predictors of candidemia in 101 pediatric ICU patients (not neonates) from the Children's Hospital of Philadelphia. They found that the presence of a CVC, a diagnosis of malignancy and receipt of either vancomycin or antimicrobials

with activity against anaerobic organisms for > 3 days were independently associated with the development of candidemia.

In agreement with the Australian study, we found prematurity and admission to an ICU as the main concomitant conditions in neonates. In children, malignancy and neutropenia were more prevalent. Neonates and children from LA were more likely to have cardiovascular disease (20.2% and 14.1%), respiratory disease (30.3% and 16.0%) and renal disease (11.2% and 15.0%) compared with the Australian patients, which reported <10% of such comorbidities. It is not possible to compare our results with Zaoutis's study, as only 33.8% of our patients, > 28 days of age, were in an ICU at the time of the incident candidemia. Furthermore, our study was designed to describe epidemiologic and clinical features of candidemia in general pediatric population in LA and was not limited to a specific group, such as ICU patients, premature infants or oncology patients—this is something that future studies in LA should aim to focus on.

In our study, we enrolled 302 candidemic patients <18 years; 89 neonates and 213 children during a 2-year period. This is 1 of the largest cohorts in the pediatric population ever published, other than the International Pediatric Fungal Network, that enrolled 221 pediatric patients with invasive candidiasis (25 neonates and 196 children) from the United States, Europe and Asia in a 5-year period, from 2007 to 2011.[22]

In both prospective, multicenter studies, non-*albicans Candida* species predominated in neonates (56% and 52%, respectively) and children (64% and 56%, respectively); nevertheless, *C. albicans* was the most common species in neonates and children in the 2 studies, followed by *C. parapsilosis*.[23–25] The 2 main differences between the studies is the high frequency of *C. tropicalis* in the present study (the third more common species in LA, compared with a low prevalence in the International Pediatric Fungal Network report), and the low frequency of *C. glabrata* in our study, similar to many pediatric reports (compared with 11% reported in children in the United States, Europe and Asia).[26,27] In agreement with other pediatric studies, many isolates from LA patients were susceptible to fluconazole.[28,29]

Survival rates at day 30 in our study were lower than those reported by other groups, 60% in neonates and 72% in children. The Australian study reported survival rates of 78% in neonates and 90% in children,[21] and the International Pediatric Fungal Network reported 92% survival in neonates and 81% in children.[22] We identified 2 independent predictors of 30-day mortality in children by multivariate analysis: renal disease and receipt of corticosteroids, different from Zaoutis *et al*[30] from the United States and Celebi *et al*[31] from Turkey who identified ICU admission as a predictor of mortality. Other independent risk factors for mortality identified in the literature in children with candidemia were disseminated candidiasis, prolonged antibiotic therapy, total parenteral nutrition, mechanical ventilation,[31] presence of an arterial catheter[30] and failure to remove a CVC.[32]

The high proportion of neonates and children with candidemia who died without antifungal therapy merits a special mention, particularly the fact that 14/17 neonates (82%) and 8/20 children (40%) who did not receive treatment died within 3 days of the incident candidemia. This observation was concentrated in a few countries and hospitals and may indicate the need of immediate interventions to improve standards in diagnostic and therapeutic strategies to improve the outcome. It is clear that either a lack of or an inadequate antifungal treatment is associated with higher mortality rates compared with timely therapy with an appropriate antifungal therapy.[33–37] Data from International Pediatric Fungal Network showed that the outcome of neonates and children with invasive candidiasis were similar in response to polyenes, azoles and echinocandins.[22] Considering these results and the high percentage of fluconazole sensitive strains in LA, the most important issue is to initiate timely therapy according to the local epidemiology data.

This study has limitations. Data were obtained from tertiary and University hospitals and therefore the immunocompromised and complex patients could be over represented in this cohort. The other limitation is that it was not possible to calculate incidence from all centers and for neonates and children separately, because in some general hospitals information on admissions and patient-days was for both adults and pediatric populations.

The active surveillance of candidemia in children in LA is a key requirement for improving disease outcome; this epidemiologic information suggests an opportunity to improve preventive, diagnostic and therapeutic strategies in our continent.

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