Etiology of fungaemia and catheter colonisation in Argentinean paediatric patients

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Summary

Yeast strains obtained from blood cultures and catheters from intensive care units (ICU) and hospitalised oncology paediatrics were studied. Yeast were the first cause of catheter colonisation (51/627), and the third cause of bloodstream infection (44/6065). In catheter, the most frequent species were *Candida albicans* (34%), *C. parapsilosis* (27.7%) and *C. tropicalis* (15%). In blood, *C. albicans* (40.8%), *C. parapsilosis* (26.6%), *C. tropicalis* (15%). *Malassezia furfur* and *Malassezia sympodialis* were isolated from catheters from ICU patients. All isolates were susceptible to amphotericin B, 88.8% to itraconazole and 91.9% to fluconazole. *Candida albicans* and *C. tropicalis* strains resistant to fluconazole and itraconazol were detected. These results reveal a change in the predominant role of *C. albicans* as cause of candidemia in hospitalised children and the emergence of antifungal resistant species. These variations emphasise the importance of performing a permanent surveillance to observe and assess them.

Key words: yeast infection, antifungal susceptibility, Argentina.

Introduction

In the last decades, the number of *Candida* species of medical importance has steadily raised and currently constitutes the dominant group of hospital-based fungal infections. *Candida* species appears as an important emerging nosocomial pathogen with other yeast previously considered innocuous and rarely associated with illness.[1–4] Important changes in the epidemiology of haematogenous candidiasis have been observed, as well as variations in the incidence of these mycoses according to different geographical regions.[5–8] Reasons for this increase include developments in immunotherapy, new surgical techniques, the availability of novel prosthetic biomaterials, the use of probes and catheters to improve life expectancy of immunocompromised patients and widespread use of broad-spectrum antimicrobial agents.[9]

Candida species are important nosocomial pathogens in critically ill children, particularly among neonates, children in intensive care units (ICU) and children with haematological illnesses. The presence of a central venous catheter and neutropenia induction during chemotherapy, as well as prolonged hyperalimentation are considered the greatest risks for subsequent fungal infection.[10–13] Likewise, immunodeficiency or long antibiotic therapies are important factors, which predispose for the development of blood stream infections by *Candida* species.[3, 14]

Since 1990, it has become clear that yeast of the genus *Candida* continue to be important etiologic agents of nosocomial blood infections. Overall, 86% of all nosocomial fungal infections and 8–10% of the nosocomial bloodstream infections have shown to be caused by *Candida* species. Furthermore, the proportion of such infections caused by non-*Candida albicans* (*C. albicans*) species is persistently rising. Nearly one-half, up to 63–88% of the cases of haematogenous candidiasis are now reported to be the result of *Candida* species other than

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albicans.[9, 15] There has been a decrease in candidemias because of *C. albicans*, an increase in the proportion of infections produced by *C. parapsilosis* and the emergence of antifungal resistance among *Candida* species.[2, 10, 12, 16]

Although mortality because of candidemia is very low among paediatric patients compared with adults, recognising predisposing factors as well as early detection and treatment of haematological infections caused by *Candida*, are the key to lower even more the risk of mortality.[12, 17]

The aim of this work was to study distribution, frequency and susceptibility profiles of yeast species causing bloodstream infection and catheter colonisation in hospitalised paediatric patients.

Materials and methods

This study was performed from September 1999 to September 2002 in Corrientes city (57°54′W and 27°55′S), located in a subtropical area in the northeast of Argentina.[18]

A total of 6065 blood samples collected by puncture of peripheral vein were studied by culture in brain–heart infusion and lyses-centrifugation method. A total of 627 venous catheters tips were collected in sterile recipients and processed by Maki and Cleri methods.[19–21] Considering in both cases, only one isolation from each patient.

Clinical specimens were collected from 1 to 15-year-old patients in ICU and hospitalised oncology patients at 'Hospital Pediátrico Juan Pablo II' from Corrientes city (Argentina). Fungal bloodstream infection was defined as a single positive blood culture for fungal pathogen. Every isolated from catheter were considered as colonisation. All specimens were processed at Hospital microbiology laboratory. Yeast isolated were sent to the Mycology Department of Instituto de Medicina Regional of Universidad Nacional del Nordeste for identification and antifungal susceptibility testing.

Kreeger van Rij methodology using physiological, biochemical and morphological tests and the API ID 32C system (bioMérieux, France) for yeast identification were applied.[22] All specimens were inoculated onto Dixon Agar and incubated at 32 °C for 7 days with daily examination for isolation of *Malassezia* spp. The identification of these fungi was carried out following the methodology suggested by Guillot *et al.* [23].

M27-A broth microdilution method standardised by the National Committee for Clinical Laboratory Standards (NCCLS) was used for *in vitro* antifungal susceptibility testing.[24, 25] The activity of amphotericin B (Squibb, NJ, USA), fluconazole (Pfizer, USA) and itraconazole (Janssen Research Foundation, Argentina) was assessed. *Candida krusei* ATCC 6258 and *C. parapsilosis* ATCC 2119 were used as quality controls. The minimal inhibitory concentration (MIC) of amphotericin B was defined as the lowest drug concentration at which there was a complete absence of growth. The MIC of the azoles were defined as the lowest drug concentrations that led to a 50% inhibition of growth in comparison with controls. The microdilution plates were determined spectrophotometrically measuring the absorbance at 405 nm.

The interpretative breakpoints were established according to recommendations of NCCLS Document M27A. For fluconazole, MICs of ≤8 μg ml^{-1} were considered susceptible, MICs between 16 and 32 μg ml^{-1} were considered susceptible dose dependent and MICs ≥64 μg ml^{-1} were considered resistant. For itraconazole, MICs of ≤0.125 μg ml^{-1} were considered susceptible, MICs between 0.25 and 0.5 μg ml^{-1} susceptible dose dependent, and MICs of ≥1 μg ml^{-1} were considered resistant. The analysis of results obtained with amphotericin B was carried out considering that 'if an amphotericin B MIC of >1 mg ml^{-1} is obtained for a *Candida* spp. isolate, then that isolate is likely resistant to amphotericin B' as stated in NCCLS Document M27-A.[24, 25]

Results

From 6.065 bloodstream studied, 376 (6.2%) were positive for different micro organisms. Yeast were isolated from 44 of 376 (11.7%) blood cultures, 34 strains were from ICU patients and 13 from oncology patients. Table 1 shows the distribution bloodstream

Table 1 Distribution of the 376 strains isolated from the positives blood cultures.

Microorganisms	*n* (%)
Streptococcus pneumoniae	87 (23.1)
Staphylococcus aureus	85 (22.6)
Yeast	44 (11.7)
Klebsiella spp.	34 (9.0)
Non-fermentative Gram-negative rods	26 (6.9)
Pseudomona aeruginosa	24 (6.4)
Enterococcus spp.	24 (6.4)
Streptococcus spp.	12 (3.2)
Enterobacter spp.	9 (2.4)
Streptococcus viridans	8 (2.1)
Escherichia coli	6 (1.6)
Gram-negative rods	6 (1.6)
Anaerobic bacteria	5 (1.4)
Bacillus spp.	4 (1.1)
Haemophylus influenzae	2 (0.5)

Table 2 Distribution of the 138 strains isolated from the positives catheters.

	n (%)
Yeast	53 (38.4)
Coagulase negative *Staphylococci*	33 (23.9)
Klebsiella spp.	18 (13.1)
Staphylococcus aureus	12 (8.7)
Non-fermentative Gram-negative rods	7 (5.1)
Pseudomona aeruginosa	6 (4.3)
Enterobacter spp.	4 (2.9)
Aerobic Gram-positive rods	4 (2.9)
Streptococcus spp.	1 (0.7)

isolates. Of 627 catheters cultured, 138 (22%) were positive for different microorganisms. Yeast were isolated from 51 of 138 (37%) of catheters. Forty-five strains were from ICU patients and nine from oncology patients. Table 2 shows the distribution of isolates from catheters. Distribution of yeast isolated from bloodstream and catheters is presented in Table 3 and Table 4 shows the distribution of yeast from ICU and oncology patients.

Associations of *Candida* species were found in four cases. One from catheter (*C. albicans* and *C. tropicalis*) and the other three from blood (*C. albicans* and *C. tropicalis*; *C. tropicalis* and *C. parapsilosis*; and *C. glabrata* and *C. parapsilosis*), which meant 47 isolates from 44 positive blood cultures and 54 isolates from 51 positive catheters. Table 5 shows the susceptibility of these isolates to fluconazole and itraconazole. According to the criteria employed, all strains were considered susceptible to amphotericin B, as MICs obtained were $<1\ \mu g\ ml^{-1}$; only *C. haemulonii* showed a MIC = $1\ \mu g\ ml^{-1}$.

Table 3 Yeast species distribution isolated from bloodstream and catheters.

	No. of isolates	
Species	Bloodstream (%)	Catheter (%)
Candida albicans	16 (34)	22 (40.8)
C. parapsilosis	13 (27.7)	14 (26)
C. tropicalis	7 (15)	9 (16.7)
C. famata	2 (4.2)	2 (3.7)
C. glabrata	5 (10.7)	3 (5.6)
C. lusitaniae	1 (2.1)	0
C. kefyr	0	1 (1.8)
C. haemulonii	1 (2.1)	1 (1.8)
C. guilliermondii	1 (2.1)	0
Malassezia furfur	0	1 (1.8)
M. sympodialis	0	1 (1.8)
R. glutinis	1 (2.1)	0
	47 (100)	54 (100)

Discussion

This study shows a high incidence of yeast infection in hospitalised children. Yeast were the first cause of catheter colonisation, and the third cause of bloodstream infection after *Streptoccocus pneumoniae* and *Staphylococcus aureus*.

While references on neonatal candidemia are frequent, few reports are found on children in ICU and oncology hospitalised paediatric patients. In this report, *C. albicans* is the most prevalent species isolated form bloodstream in ICU but <50% of the cases, standing out non-*C. albicans* species as predominant opportunistic pathogens. It should be noted that blood cultures from oncology patients revealed a very low prevalence for *C. albicans*. Both results differ from previous reports

Table 4 Yeast species isolated from bloodstream and catheter from intensive care units (ICU) and oncology patients.

	UTI		Oncology patients	
Species	Bloodstream (%)	Catheter (%)	Bloodstream (%)	Catheter (%)
Candida albicans	15 (44.1)	21 (46.7)	1 (7.7)	1 (11.1)
C. parapsilosis	8 (23.6)	12 (26.7)	5 (38.5)	2 (22.2)
C. tropicalis	7 (20.7)	9 (20)	0	0
C. famata	1 (2.9)	0	1 (7.7)	2 (22.2)
C. glabrata	1 (2.9)	1 (2.2)	4 (30.7)	2 (22.2)
C. lusitaniae	1 (2.9)	0	0	0
C. kefyr	0	0	0	1 (11.1)
C. haemulonii	0	0	1 (7.7)	1 (11.1)
C. guilliermondii	0	0	1 (7.7)	0
Malassezia furfur	0	1 (2.2)	0	0
M. sympodialis	0	1 (2.2)	0	0
R. glutinis	1 (2.9)	0	0	0
	34 (100)	45 (100)	13 (100)	9 (100)

Table 5 Fluconazole and itraconazole susceptibility tests.

		Itraconazole			Fluconazole		
	n	Susceptible (%)	S-DD* (%)	Resistant (%)	Susceptible (%)	S-DD* (%)	Resistant (%)
Candida albicans	38	37 (97.4)	1 (2.6)	0	37 (97.4)	0	1 (2.6)
C. tropicalis	16	13 (81.3)	3 (18.7)	0	15 (93.7)	0	1 (6.3)
C. parapsilosis	27	27 (100)	0	0	27 (100)	0	0
C. famata	4	4 (100)	0	0	3 (75)	1 (25)	0
C. glabrata	8	4 (50)	2 (25)	2 (25)	6 (75)	0	2 (25)
C. haemulonii	2	0	0	2 (100)	0	2 (100)	0
C. lusitaniae	1	1 (100)	0	0	1 (100)	0	0
C. kefyr	1	1 (100)	0	0	1 (100)	0	0
C. guilliermondii	1	1 (100)	0	0	1 (100)	0	0
R. glutinis	1	0	0	1 (100)	0	0	1 (100)
All yeast	99	88 (88.8)	6 (6.1)	5 (5.1)	91 (91.9)	3 (3)	5 (5.1)

S-DD, susceptible dose dependent.

from Argentina and other countries where *C. albicans* usually exceeds 50% of the isolates.[12, 17, 26–28]

Candida parapsilosis is recognised as a nosocomial pathogen of great relevancy and mainly responsible of infection in Oncology patients and newborns at Neonatal ICU.[12, 13, 26, 29, 30] In the present work, this was the most frequent yeast that has isolated from bloodstream of the hospitalised children and the second cause of bloodstream infection in ICU.

In this study, the frequency of *C. tropicalis* isolates from bloodstream of children in ICU is significant, assuming that this species is more invasive than *C. albicans* and tends to become resistant to azoles.[31, 32]

The percentage and the low susceptibility of *C. glabrata* isolated from Oncology patients' blood cultures is important taking into account that it has been reported as a major nosocomial pathogen in adults and as emergent in paediatric patients, among whom it causes high mortality because of the development of secondary resistance to fluconazole.[2, 3, 5, 33, 34]

In European and USA Oncology paediatric Units, blood cultures yeast prevalence differs from our results. They present a higher percentage of *C. albicans* and *C. glabrata*, and also detect *C. tropicalis* which was not found in our Oncology patients.[4, 5, 11, 35]

The most frequent catheters colonizer in ICU was *C. albicans* followed by *C. parapsilosis* and *C. tropicalis*. The propensity of those species to form a slime in glucose-containing solutions suggest that this phenotypic characteristic enables them to adhere to plastic catheters and to be a case of infections in individuals receiving intravenous hyperalimentation.[30, 36, 37] In oncology patients, we did not find predominance of any species. These findings differ with percentages previously reported by other authors.[2, 11, 15, 29] Probably, lack of infection surveillance and environment control in these critical units may be the reasons of the high rate of yeast founded. It would be of interest to study the horizontal transmission of this fungi through direct interaction between nurses and children, as we think that hospitalised patients may acquire *Candida* spp., particularly *C. parapsilosis*, via the health-care workers' hands.

The isolation of *Malassezia furfur* and *Malassezia sympodialis* from catheters in ICU is relevant as they have been referred as producers of fungemias in paediatric patients with parental lipid hyperalimentation.[38–42] As these organisms do not develop in routine culture medium, because of their nutritional requirements, we concluded is important to introduce changes in the current laboratory methodology in order to enable their isolation avoiding subdiagnosis.

Amphotericin B resistant *C. haemulonii* with high MIC for fluconazole was reported causing fungaemia.[43, 44] In this study, *C. haemulonii* isolated from one oncology patient, showed borderline MIC for amphotericin B (1 μg ml^{-1}), resistance to itraconazole and high MIC for fluconazole.

Because there are no previous similar studies neither in this Hospital nor in this area, the role of prior azole antifungal exposure and its impact on susceptibility profile and in a shift in *Candida* species isolated from blood cultures, cannot be discussed.

As reported in other countries for paediatric patients, most of *Candida* species isolated in this work were susceptible to azolic antifungal agents.[3, 5, 15, 45–47] Resistant strains to fluconazole and susceptible dose dependent strains to itraconazole were detected, indicating an emergent triazolic cross resistance or a tendency to develop it. As, antifungal therapeutic options for

paediatric patients are very scarce, careful analysis of risk factors, regular control of yeast colonisation, correct identification of etiological agents and *in vitro* susceptibility tests study are extremely important in hospitalised paediatric patients in order to establish an effective therapeutic and a preventive strategy that can be really efficient.

Results of this work reveal an important rate of infection with yeast in hospitalised paediatrics patients, but they are not comparable with few previous reports from our country because we worked with strains belonging to risk patients (UCI and Oncology). Those reports do not specified the Units from which the population studied came.[45, 48] Even if, the rate would have been different because prevalence of candidiasis diverges greatly between distinct studies. The reason for this is unknown, but it is assumed that is related to multiple factors, including population of patients, use of antimicrobial agents, cytotoxic chemotherapy and underlying illnesses as well as antifungal therapy.

Our results suggest a change in the role frequently assigned to *C. albicans* as a cause of candidemia in hospitalised children. This epidemiological characteristic and the detection of antifungal resistant species emphasise the importance of performing a permanent surveillance, to assess these variations and to detect emergence of resistance.

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