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PEDIATRIC FUNGAL INFECTIONS (T LEHRNBECHER, SECTION EDITOR)

Important Mycoses in Children in South America

Fabianne Carlesse[1] · **Adriana Maria Paixão de Sousa da Silva**[2] · **Maria Elena Santolaya**[3]

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Abstract Invasive fungal disease (IFD) is an important infection with high rates of morbidity and mortality in hospitalized patients. Data on incidence, risk factors, and mortality of IFD in the pediatric population, mainly in South America, are scarce. The aim of this paper was to review the literature about the most important IFD in pediatrics in South America. We searched three electronic databases (Medline, Lilacs, and Cochrane databases) for studies published between 2012 and 2015; case reports and editorial were excluded. Twenty-two articles were found on *Candida* spp. infections; eight on *Paracoccidiodes* spp.; two on *Cryptococcus* spp.; and one on *Aspergillus* spp. *Candida albicans* was the main agent, followed by *Candida parapsilosis* in pediatric population. *Paracoccidioides* spp. had a prevalence ranging from 2.3 to 35.3 % with ages between 11 and 29 years, malnutrition, and hepatic involvement related to the worst prognosis. *Cryptococcus* spp. showed a prevalence of 2.6 % in under 16 years old, with cryptococcal meningitis most observed, mainly by *Cryptococcus neoformans* (94.1 %). Aspergillosis and other mold infections, as zygomycosis and fusariosis occurring mostly in immunocompromised children, related with relevant morbidity and mortality in this population.

Keywords Mycoses · Children · South America · Fungal infection · Pediatric fungal infections

Introduction

Invasive fungal disease (IFD) is a relatively common and potentially lethal infection in hospitalized children, especially in patients with serious underlying diseases such as hematological malignancies or critically ill patients hospitalized in intensive care units (ICUs), that prolong hospital stay, have elevated morbidity and mortality rates, and increase medical care costs. Multiple surveillance networks have documented a high incidence of pediatric fungal bloodstream infections [1] especially in susceptible hosts [2, 3]. IFD are the leading infectious cause of death in children with cancer or following an organ or hematopoietic stem cell transplant (HSCT) [4, 5]. The case fatality rate associated with pediatric fungal sepsis is 13 %, the second highest rate of all causes of sepsis in children in USA [6].

Studies describing the epidemiology, clinical and laboratory characteristics of IFD have been performed mostly in adult populations [7]. There are some differences in risk factors and features for IFD between adults and children, and the use of adult data to manage these infections in pediatric setting may be inappropriate. Apart from this, the incidence and epidemiology of IFD may differ significantly depending on the geographic region [8]. Data on incidence, risk factors, and mortality of IFD in the pediatric population in South America are scarce. The knowledge of these epidemiological differences to implement appropriate strategies of prevention, diagnosis, and therapy is noteworthy. The aim of this paper is to review the

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✉ Fabianne Carlesse
fabiannecarlesse@graacc.org.br

[1] GRAACC-Instituto de Oncologia Pediátrica, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil

[2] Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil

[3] Infectious Diseases Unit, Department of Pediatrics, Hospital de niños Dr. Luis Calvo Mackenna, Faculty of Medicine, Universidad de Chile, Santiago, Chile

literature about the most important IFD in pediatrics in South America.

Methods

Three electronic databases were searched (Medline, Lilacs, and Cochrane databases) for studies published between 2012 and 2015 with the following MeSH terms: invasive mycoses, mycoses, invasive fungal infection, yeast infection, mold infection, *Candida* infection, pediatric fungal infections, children, America, and South America. There were no language restrictions for these searches.

For inclusion, the studies had to have results of IFD in pediatric patients (0 to 18 years old) from South America. Case reports and editorials were excluded (Fig. 1).

Of the studies identified in the updated review, 22 were on *Candida* spp. infections [8–29] (five articles only in neonatal patients), 8 on *Paracoccidiodes* spp. [30–37], 2 about *Cryptococcus* spp. [38, 39], and 1 on *Aspergillus* spp. [40]. The other selected studies were about the following topics: one epidemiological descriptive study [41], one identified risk factors associated with IFD in patients with cancer [42], one about prophylaxis [43], and one related with the environment as a source of mold infections in pediatric patients with cancer [44].

Main studies included in this revision are shown in Table 1 (candidiasis, paracoccidiodomicosis, cryptoccocosis, aspergillosis, and others)

Candida spp.

Candida spp. is a commensal microorganism that naturally inhabits various sites in the human body (including the gastrointestinal and respiratory tracts) and in part of the vaginal and urethral microbiota. These microorganisms can become pathogenic as a result of alterations in host defense mechanisms or breakdown of anatomical barriers—situations that are common in hospitalized patients who receive antibiotics or undergo frequent invasive procedures. Candidemia often occurs in patients admitted to neonatal or surgical ICUs [46].

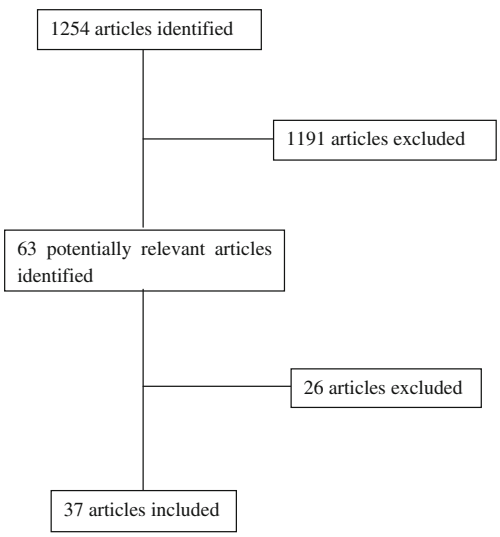

Fig. 1 Flow diagram for invasive fungal disease in South America update review

Candida species are the third most common cause of pediatric health care-associated bloodstream infection in the USA and Europe. The attributable mortality from invasive candidiasis in children is 10 %, and invasive candidiasis is associated with prolonged hospital stay and increased costs [47]. Inappropriate antifungal therapy and the occurrence of infections by resistant species can impact mortality rate.

The epidemiology of such infections varies among different geographic regions and even between medical centers within the same region with temporal variability [48–51]. The Global Antifungal Surveillance Program, ARTEMIS DISK, analyzed a total of 256,882 *Candida* isolates obtained from 142 medical centers in Asia, Latin America, Europe, Africa, and North America between 1997 and 2007, showing that the most common species globally was *Candida albicans* (65.3 %), followed by *Candida glabrata* (11.3 %), *Candida tropicalis* (7.2), *Candida parapsilosis* (6.0 %), and *Candida krusei* (2.4 %). These five *Candida* spp. are important worldwide, but their frequency varied significantly according to the setting [50, 51].

Little is known about the epidemiology of candidemia in South America, especially in pediatric patients. Currently, there are 22 studies about this infection which include children [8–29]. From these, only three included exclusively pediatric patients [14, 22, 26] and from these two followed patients with candidemia [22, 26] and only one analyzed samples of *C. parapsilosis* from blood [14], 11 studies included adult and pediatric patients [8, 10–13, 15, 16, 18, 23, 24, 27], 5 studied included only neonates [19–21, 28, 29], 3 were articles about review [25] and recommendations [21, 28], 1 did not informed the age of the patients [16], and 1 was on samples collected from health professionals and the environment [9] (Appendix 1).

C. albicans was reported as the most common species causing candidemia an epidemiological shift toward non-*albicans* [51]. In Brazil and some other countries in Latin America, *C. parapsilosis* is responsible for 20–30 % of nosocomial candidemias in general population [52].

Analyzing the two studies performed in Latin America (LA) which enrolled only pediatric patients, the first was a prospective, multicenter study of active surveillance candidemia in seven countries in LA. This study enrolled 302 patients under 18 years, 89 neonates and 213 children during a 2-year period. Non-*albicans Candida* species predominated in neonates and children; *C. albicans* alone was

Table 1 Studies included in the revision

Year	Author	Country	Study designed	Period	Population	Total of patients % of children	Main species	Risk factor or factors associated	Site of isolation	Mortality
Studies on invasive candidiasis in pediatric patients in South America										
2012	Storti et al. [9]	Brazil	Sample collection	March–November 2008	Pediatric unit	*N* = 13 Pediatrics 4%	*C. albicans* 53.8% *C. tropicalis* 23.1% *C. parapsilosis* 7.7% *C. krusei* 7.7% *C. guilliermondii* 7.7%	Pediatric ICU	Blood, urine	23.1%
2012	Yamamoto et al. [10]	Brazil	Retrospective	2008–2009	*N* = 91 29days to 82years	*N* = 23 <1year 23%; 1 to 4 1%; 5 to 14 2%	–	Neonatal ICU 25%, prematurity and low weight	Blood, urine, fluids, secretion, BAL, and swab	–
2012	Bonfietti et al. [11]	Brazil	Prospective	1998–2007	*N* = 100	*N* = 74 Pediatrics 74.2%	–	Neonatal ICU 29.2%	Blood	59%
2013	Almeida et al. [12]	Brazil	Prospective	2010–2011	*N* = 50 <1 to >61years	*N* = 15 <20years 30%	–	<1year 22%; >61years 46%	Blood, urine	–
2013	Colombo et al. [13]	Brazil	Prospective	2006–2007	*N* = 300 0–96years	*N* = 61 NB 5.3%; ≤13years 15%	–	Child	Blood	–
2013	Ruiz et al. [14]	Brazil	Transversal	1999–2003	0–15years	*N* = 49	*C. parapsilosis* 83.7% *C. orthopsilosis* 10.2% *C. metapsilosis* 6.1%	Biofilm	Blood	
2013	Nucci et al. [8]	Brazil, Chile, Ecuador, Argentina, Colombia, Venezuela, Honduras, Mexico	Prospective	2008–2010	*N* = 672 0–98 years	*N* = 297 <1year 23.7%; 1 to 18years 20.5%	*C. albicans* (43.8% NB/ 48.6% 1month–11years/ 29.7% 12–18years) *C. parapsilosis* (27% NB/ 24.3% 1months–11years/ 28.3% 12–18years) *C. tropicalis* (14.6% NB/ 8.6% 1months–11years/ 15.9% 12–18years) *C. guilliermondii* (4.5% NB/ 15.7% 1months–11years/ 11.6% 12–18years) *C. glabatra* (3.4% NB/1.4% 1months–11years/3.6% 12–18years) *C. krusei* (4.5% NB/3.6% 1months–11years/3.6% 12–18years)	NB and 1 to 11years	Blood	NB 40.3% 1 to 11years 20.7% 12 to 18years 20.3%
2013	Wille et al. [15]	Brazil	Prospective	1994–2004	*N* = 388 0–99years	*N* = 66 17%	–	Pediatric ICU	Blood	55.4% not stratified by age
2013	Moretti et al. [16]	Brazil	Retrospective	2006–2010	*N* = 313	*N* = 24 1 to 14years 7.9%	–	–	Blood	–
2013	Santolaya et al. [17]	–	Recommendation	–	Children	–	–	–	–	–
2013	Hoffman et al. [18]	Brazil	Retrospective	2006–2011	*N* = 130 0 to ≥60years	*N* = 50 13.1% children; 25.4% NB	*C. albicans* (43.8% NB/ 35.7% children) *C. parapsilosis* (27% NB/ 26.3% children)	Prematurity, ICU, malignancy, neutropenia, TPN, neurological disease,	Blood	NB 40% Children 28%

Table 1 (continued)

Year	Author	Country	Study designed	Period	Population	Total of patients % of children	Main species	Risk factor or factors associated	Site of isolation	Mortality
							C. tropicalis (14.6% NB/ 14.6% children) *C. guilliermondii* (4.5% NB/ 12.7% children) *C. glabatra* (3.4% NB/3.3% children)	respiratory disease, IMV, corticosteroids		
2013	Tinoco et al. [19]	Brazil	Epidemiological	2years	NICU	*N* = 295 Candidiasis 5.4%; colonization 80%	Colonization—albicans 70.7%; glabatra 6.1%; krusei 3%	First 25days of hospitalization, WB <1.5kg. Colonization—mother >23years, GA >30weeks	–	–
2013	Ruiz et al. [20]	Brazil	Transversal	43days	7–60days NICU	*N* = 11	*C. parapsilosis*	–	Blood	–
2013	Santolaya et al. [21]	–	Recommendation	–	NB	–	–	–	–	–
2013	Santolaya et al. [22]	Argentina, Brazil, Chile, Colombia, Ecuador, Honduras, Mexico, and Venezuela	Prospective	2008–2010	*N* = 302 <18years	NB 29%, children 71%	*C. parapsilosis* (42.4% NB/ 45.8% children) *C. albicans* (36.4% NB/ 35.4% children) *C. tropicalis* (15.1% NB/ 12.5% children)		Blood	–
2014	Maldonado et al. [23]	Colombia	Prospective, case control	2010–2011	*N* = 300 0–94years	*N* = 61 NB 11.4%; children 9.16%			Blood, sterile fluid, tissues	19.8% not stratified by age
2014	Cortés et al. [24]	Colombia	Transversal	2008–2009	*N* = 131 9days to 87years	*N* = 27 NB 11.4%, children 9.16%	*C. albicans* (60% NB/67% children) *C. parapsilosis* (13.3% NB/ 33% children) *C. tropicalis* (13.3% NB)		Blood	28%
2014	Quindós [25]	–	Review	–	–	–				–
2014	Oliveira et al. [26]	Brazil	Prospective	2007–2010	5 to 11years	*N* = 104	*C. albicans* 37.5%; *C. tropicalis* 24.03%; *C. parapsilosis* 22.11%; *Pichia anomala* 5.8%; *C. guilliermondii* 4.8%; *C. krusei* 2.88%; *C. glabrata* 1.92%; C. *pararugosa* 0.96%		Blood	
2014	Costa et al. [27]	Brazil	Prospective	2006–2007. 201-2011	*N* = 108 0 to ≥60years	*N* = 35 NB 22,7%; ≤1–18years 13.4%	NB: albicans 34.6%; tropicalis 13.8%; parapsilosis 34.8%	Prematurity 19.6%	Blood	
2014	Izquierdo et al. [28]	Chile	Recommendation	–	NB	–		<28weeks, <1000g, cephalosporins Third or fourth generation, carbapenems, H2 blockers, necrotizing	–	–

Table 1 (continued)

Year	Author	Country	Study designed	Period	Population	Total of patients % of children	Main species	Risk factor or factors associated	Site of isolation	Mortality
								enterocolite, CVC, IMV, multiple colonization ≥3 sites		
2014	Batista et al. [29]	Brazil	Prospective	October 2006–March 2007	NICU; WB < 1.5kg	*N* = 125 Oral colonization 15.2%; Fungemias 9.6%	Colonization—*C. albicans* 68.4%; *C. parapsilosis* 10.5%; *C. krusei* 10.5%; *Trichosporon asahii* 5.3%; *Rhodotorula rubra* 5.3%. Fungemias—*C. albicans* 50%; *C. parapsilosis* 33.4%; *Pichia anomala* 8.3%; *Pichia angusta* 8.3%	–	Swab and blood	66.60%
Studies on paracoccidioidomicosis in pediatric patients in South America										
2012	Matos et al. [30]	Brazil	Series of cases	1997–2007	*N* = 216 3–71years	*N* = 39 0–19years 18.5%	–	–	–	–
2013	Bellissimo-Rodrigues et al. [31]	Brazil	Retrospective	1970–2009	*N* = 1219 3–85years	*N* = 154 <21years 12.6%	–	–	–	–
2013	Marques et al. [32]	Brazil	Prospective	–	*N* = 695 2–90years	*N* = 334 2–10years 11.1%; 11–20years 31.6%	–	–	–	–
2013	Braga et al. [33]	Brazil	Retrospective and prospective	1980–2010	<16years	*N* = 102	–	Liver involvement	–	4.8%
2014	Fabris et al. [34]	Brazil	Series of cases and prospective	1980–2009	*N* = 595 4–94years	*N* = 13–51 0–19years 2.3–8.7%	–	–	–	–
2014	Taicz et al. [35]	Argentina	Series of cases	2000–2010	3–9years	*N* = 4	–	–	–	–
2014	Vieira et al. [36]	Brazil	Epidemiological	1997–2012	*N* = 2163 3–82years	*N* = 55 <1years 2.1%; 15–19years 0.5%	–	–	–	–
2014	Magalhães et al. [37]	Brazil	Prospective	May–December 2009	*N* = 542 11–86years	*N* = 147 11–29years 35.37%	–	11–29years	–	–
Studies on criptococcosis in pediatric patients in South America										
2012	Quian et al. [38]	Uruguay	Series of cases	1990–2011	7–13years	*N* = 3	*C. neoformans* 100%	HIV 100%	Neurocryptococcosis 100%	–
2014	Lizarazo et al. [39]	Colombia	Transversal	1993–2010	<16years	*N* = 1578	*C. neoformans* 94.1%; *C. gattii* 5.9%	HIV 24.4%; autoimmune disease 7.3%; use of corticosteroids 7.3%; hematologic disease 7.3%; kidney disease 2.3%; solid tumor 2.3%; prematurity 2.3%	Neurocryptococcosis 87.8%; disseminated 12.2%	–
Studies on *Aspergillus* spp. in pediatric patients in South America										
2014	Fernández et al. [40]	Argentina	Transversal	2011	ICU and burn unit	*N* = 96 strains	BU: clavatus 3.84%; flavus complex 26.93%;	Spring	–	–

Table 1 (continued)

Year	Author	Country	Study designed	Period	Population	Total of patients % of children	Main species	Risk factor or factors associated	Site of isolation	Mortality
							fumigatus complex 3.84%; niger complex 26.93%; ochraceus 3.84%; parasiticus 3.84%; sydowii 23.09%; terreus complex 7.69%. ICU: flavus complex 3.92%; fumigatus complex 5.88%; nidulans complex 1.96%; niger complex 29.42%; ochraceus 7.84%; parasiticus 3.92%; sydowii 25.50%; terreus complex 9.80%; ustus complex 3.92%; versicolor complex 3.92%; unguis 3.92%			
Others										
2010	Villarroel et al. [45]	Chile	Prospective, multicenter	2004–2006	*N* = 646 <18years of age Children with cancer, fever, and neutropenia	*N* = 646 100%	*Candida* spp. *Aspergillus* *Zygomicetes* *Fusarium*	Combination of fever, AMC < 100/mm^3 and CRP > 90mg/L at day 4 of therapy for a febrile neutropenic episode provided a RR for IFD of 5.4 (99% CI 3.2–9.2)	Blood Lung, sinus, and skin biopsy	23%
2012	Moral et al. [41]	Argentina	Prospective	2005–2008	*N* = 1020 0–99years	*N* = 295 <19years 29%	*Candida* < 1year: *albicans* > *parapsilosis* > *tropicalis* > *glabatra*; 1 to 19: *albicans* > *parapsilosis* > *tropicalis*	Prematurity	Blood	–
2013	Nucci et al. [42]	Brazil	Prospective	2007–2009	*N* = 937 0–82years AML/MDS or HCT	*N* = 60 <18years 6.5%	IFD	–	–	–
2012	Rabagliati [43]	Chile	Prophylaxis	–	Solid organ transplantation and hematopoietic precursors	–	–	–	–	–
2013	Mesquita-Rocha et al. [44]	Brazil	Prospective	2007–2008	*N* = 164 HSCT pediatrics	*N* = 139 Filamentous fungi 84.8%	*Mycelia*, *Cladosporium*, *Penicillium*, *Purpureocillium*, *Aspergillus*	Autumn and summer, water temperature	Water samples	4.8%

the main specie (43.8 % neonates and 35.7 % children), followed by *C. parapsilosis* (27 % neonates and 26.3 % children) [8]. Comparing this study with the other largest study published in 2012 by the International Pediatric Fungal Network, which enrolled 221 pediatric patients with invasive candidiasis (25 neonates and 196 children) in the USA, Europe, and Asia over a 5-year period from 2007 to 2011 [53], the two main epidemiological differences are the high frequency of *C. tropicalis* and the low frequency of *C. glabrata* in LA.

Another study from LA, performed in Brazil, analyzed the frequency of yeasts of the genus *Candida* over a 4-year period, isolated from 104 patients from 5 to 11 years of age, admitted to a public hospital of the city of Sao Paulo, Brazil. In this study, non-*albicans species* predominated (63.5 %) and *C. tropicalis* was slightly more frequent than *C. parapsilosis* (24.03 and 22.11 %, respectively). On the contrary in LA study, *C. parapsilosis* was more frequent than *C. tropicalis* (26.3 vs 14.6 %) [26].

This high prevalence of *C. parapsilosis* in pediatric patients could be explained by the fact that this species is related to prematurity, presence of central venous catheters, use of total parenteral nutrition [53], and the use of mechanical ventilation [11]. The high prevalence of *C. parapsilosis* and *C. tropicalis* as etiologic agents of candidemia in LA has been recorded in other studies which include children and adults [52, 54]. Candidemia by *C. tropicalis* related with a worse prognosis compared with candidemia by other species in neutropenic patients [11].

Anatomical and physiological differences between the pediatric and adult patients change the susceptibility to infections caused by different species of *Candida*, which therefore influences the antifungal treatment approach, including issues related to the toxicity of the drugs, pharmacokinetic, and dosage [55]. Data regarding the pattern of resistance of etiologic agents is a powerful tool to guide prophylactic, preemptive, and empiric antifungal therapy [56, 57]. Bonfietti et al. in 2012 evaluated the incidence and susceptibility profile of *Candida* spp. causative agents of bloodstream infections in a Brazilian tertiary care hospital. They found that *C. albicans*, *C. parapsilosis*, and *C. tropicalis* isolates presented high susceptibility to all antifungal agents tested. The highest fluconazole MICs were observed for *C. parapsilosis* isolates from two patients who were successfully treated with amphotericin B or fluconazole monotherapy [11]. Recommendation for antifungal therapy in neonates and children with IC in LA is described in Table 2.

Paracoccidioidomycosis

Paracoccidioidomycosis (PCM) is a systemic infection caused by the dimorphic species of fungus *Paracoccidioides brasiliensis* or *Paracoccidioides lutzii* which can exist as a mycelia stage and yeast [58]. The mycelia form is found in nature at temperatures between 18 and 25 °C and produces spores or yeast-like conidia which may cause infections. Spores inhaled by susceptible hosts are converted into yeast in the tissues. By inhalation, spores target the lungs and later on reach any systemic structure through the lymphatic or blood stream, especially affecting skin, mucus membranes, lymphatic tissue, and adrenal glands [59, 60]. Traumatic inoculation, in which the fungus settles on the skin mucosa, can also occur. In most individuals, the disease is self-limited and asymptomatic because of appropriate cellular immune responses [61].

The distribution of this disease is heterogenous showing high and low endemicity in different areas in accordance with climate and the environmental condition in the region. In LA, PCM is considered one of the most important systemic mycoses [36], with Brazil, Venezuela, and Argentina the countries with the greatest number of cases. Over than 80 % of Paracoccidioidomycosis cases worldwide are from Brazil where PCM is the eighth leading cause of death from chronic infectious and parasitic diseases with the highest mortality rate among systemic mycoses with a mean annual mortality rate from 1980 to 1995 was 1.45/million inhabitants [62]. Reports of cases in nonendemic areas are related to people who had lived or visited endemic areas before the beginning of signs and symptoms of the disease [58].

The disease exhibits many clinical presentations, which may be roughly classified into two forms: acute/subacute and chronic. Diversity of clinical presentation has been attributed to the enhanced pathogenicity of some *P. brasiliensis* strains and particularly to host factors that modulate the immune response against the fungus [63, 64].

This infection is more commonly acquired between the first and second decades of life. Progression to the systemic form in this period of the life is rare, between the third and fifth decades of life, the disease is activated, causing the chronic form of PCM [65]. Children and young adults most frequently present with acute/subacute form of the disease (juvenile type), which is a more widespread disease, involving the lymphohematopoietic system (mainly liver) [66, 67]. Older patients generally have a chronic form of the disease (adult type), which affects primarily the lungs and upper airway [60]. Another factor that is important to note is the decrease of the disease in females as they get older. In the prepuberal age, PCM has been known to occur in similar proportions in boys and girls, with a gender ratio of 1.7:1.0. After menarche, women become less susceptible to PCM due to the presence of estrogens, which slowly inhibits the transformation of filamentous phase, the infective, pathogenic yeast phase. In this way, the chronic form is much more prevalent in men, with a gender ratio of 15:1 [68, 69].

In our review, we found eight articles of PCM, mainly from Brazil (seven) [30–34, 36, 37] and one from Argentina [35].

Table 2 Recommendations for the management on invasive candidiasis in pediatric patients in Latin America adapted from Santolaya ME et al., 2013

Management		Children with neutropenia	Children without neutropenia:	Neonates
Prophylaxis		Patients with high risk of *Candida* infections associated with a high incidence of IFD	Patients underwent to high-risk liver transplant, abdominal surgery	Low birth weight (<1000 g) and extreme prematurity (<28 weeks)
		Fluconazole, 6 m/kg/day for children ≤30 kg and 400 mg/day for children >30 kg		Fluconazole (3 mg/kg twice weekly for 6 weeks)
		Alternative: micafungin, 1 mg/kg (IV) 1×/day		
		High levels of species fluconazole resistant		
Empirical treatment		Search for IC in patients with fever and neutropenia over 4 days of antimicrobial therapy	No recommendations can be made	No recommendations can be made
		Start antifungal treatment for children at high risk for IFD: patients with AML, leukemia relapse, mucositis, typhitis		
		Equinocandins or L-AmB		
Treatment	First line	Caspofungin IV, 70 mg/m^2/day (day 1), followed by 50 mg/m^2/day or micafungin IV, 2–4 mg/kg/day	Caspofungin IV, 70 mg/m^2/day (day 1), followed by 50 mg/m^2/day or micafungin IV, 2–4 mg/kg/day or L-AmB, 3 mg/kg/day	AmB (either d-AmB or L-AmB) or an echinocandin (caspofungin or micafungin)
	Alternative	L-AmB (IV), 3–5 mg/kg/day or voriconazole IV, 14 mg/kg/day BD or PO, 200 mg BD.	Lipid formulations AmB or d-AmB or fluconazole	
	Management	Treat for 14 days after the first negative blood culture and resolution of clinical signs	De-escalation to oral fluconazole when the patient is stable, and *Candida* spp. is susceptible	CNS involvement should be ruled out prior to echinocandin use. Fluconazole is recommended for the treatment of urinary tract candidiasis in neonates
Workup		Abdomen image exam, fundoscopy, ecocardiography		

Source: [17, 21]

d-AmB deoxicolate amphotericin B, *L-AmB* liposomal amphotericin B, *IV* intravenously, *PO* orally, *IC* invasive candididiasis

From these, four were prospective studies [32–34, 37], one retrospective [31], two case series [30, 35], and one descriptive [36] (Appendix 2). The described prevalence of this disease from 0 to 29 years ranged from 2.3 to 35.3 %. Three variables were related to a worse prognosis: age between 11 and 29 years, malnutrition, and hepatic involvement [33, 37]. Major clinical manifestations were generalized lymphadenopathy (95.1 %), weight loss (82.9 %), fever (78 %), asthenia (63.4 %), splenomegaly (58.5 %), pallor (56.1 %), and increased abdominal circunference; 40.1 % had liver involvement with hepatomegaly detected by physical examination in 68.3 % of them [33]. Anemia, leukocytosis, eosinophilia, hypoalbuminemia, hypergamma globulinemia, and increased erythrocyte sedimentation rate (ESR) were the most frequent laboratory findings [33, 37].

The definitive diagnosis was made by histopathological findings in most cases, followed by culture [33, 35]. Two studies evaluated the intradermal reaction (gp43) and showed a poor sensitivity; the exam was positive in 35.4 to 42.7 % of patients between 0 to 29 years of age. None had clinical manifestations [32, 37].

The treatment of PCM includes supportive care and specific antifungals. *P. brasiliensis* is susceptible to the majority of antifungals: amphotericin B, azoles: fluconazole, itraconazole; ketoconazole, voriconazole, and sulfametoxazole/trimethoprim (TMT/SMX) [61].

Limited data exists comparing the different therapeutic approaches. Itraconazole is recommended for the mild forms due the short time required to control the disease. Patients with severe disease or intolerance to azoles must receive amphotericin B or TMT/SMX intravenously as inpatient. TMT/SMX was the main drug used in children younger than 10 years old due to the simple administration and tolerance [60].

Voriconazole can be recommended for patients with central nervous system (CNS) involvement due to its effectiveness [60].

In a clinical and laboratory study on pediatric patients with and without hepatic involvement, trimethoprim–sulfamethoxazole was the main drug used (26/41). An association with amphotericin B, ketoconazole, or itraconazole was necessary in 13/41 cases. The remaining patients ($n=2/41$) received a single drug treatment with amphotericin B [33]. Another pediatric series from Argentina used amphotericin B as first choice (3/4) because of severity of the disease followed by itraconazole to complete treatment. All patients survived [35]. The duration of treatment is around 12 months and depends on clinical and serological response [60]. Recommendation for antifungal therapy in children with paracoccidiodomicosis is described in Table 3.

Cryptococcosis

Cryptococcosis is a systemic fungal disease associated with high lethality. It is caused by *Cryptococcus* spp. which is an encapsulated fungus that was considered an unusual pathogen before 1955 and became a frequent opportunistic microorganism worldwide, as the population of immunocompromised people increased [70]. Two species of *Cryptococcus* are the most relevant to human health: *Cryptococcus neoformans* and *Cryptococcus gattii*. The first has worldwide distribution and is related to pigeon droppings, being more frequent in patients with HIV/AIDS; by contrast, *C. gattii* is mainly distributed in trees as *Eucalyptus camaldulensi* of tropical and subtropical regions [71].

After the inhalation of viable airborne spores of these yeasts directly from the environment, *Cryptococcus* spp. invades the lung tissue and then a hematogenous dissemination occurs, with a predisposition for the CNS [72]. However, there are observations suggesting that infections by *Cryptococcus* spp. can be asymptomatic and frequent in the early years of life [73]. The disease may occur in immunocompetent

Table 3 Recommendations for management on paracoccidiodomicosis in pediatric patients adapted from Shikanai-Yasuda MA, 2006

Clinical Presentation	Drug		Dosage	Duration
Mild and moderate form—outpatients	First line	Trimethoprim/sulfametoxazole	Trimethoprin, 8 to 10mg/kg and sulfametoxazole, 40 to 50mg/kg (PO) 12/12h	12months on mild forms and 12 to 24 months on moderate forms
	Alternative	Itraconazole	Weighing <30kg and > 5years old 5 to 10mg/kg/day (PO)	6 to 9 months on mild forms and 12 to 18 months on moderate forms
Severe forms (disseminated disease, CNS accomitiment, respiratory failure, jaundice, hemodynamic instability)—inpatient	First line	Trimethoprim/ sulfametoxazole	Trimethoprin, 8 to 10mg/kg and sulfametoxazole, 40 to 50mg/kg, IV, BID/QD	Change for oral drug when it will be possible
	Alternative	Amphotericin B	1mg/kg/day (IV)	

Source: [60]

IV intravenously, *PO* orally

Table 4 Recommendations for management on cryptococosis in pediatric patients adapted from Perfect J, 2010

Clinical presentation	Management
Induction and consolidation therapy for CNS and disseminated disease	d-AmB (1 mg/kg/day IV) plus flucytosine (100 mg/kg/day orally in four divided doses) for 2 weeks
	Non-HIV-infected, nontransplant population, followed by therapy with fluconazole (10–12 mg/kg per day orally) for 8 weeks
	For d-AmB intolerant patients, either L-AmB (5 mg/kg/day) or ABLC (5 mg/kg/day)
	Maintenance therapy is fluconazole (6 mg/kg/day orally)
	Discontinuation of maintenance therapy in children receiving HAART is poorly studied and must be individualized
Cryptococcal pneumonia	Fluconazole (6–12 mg/kg/day orally) for 6–12 months

Source: [82]

d-AmB deoxicholate amphotericin B, *L-AmB* liposomal amphotericin B

individuals but is more frequent in immunocompromised patients mainly with HIV/AIDS who had impairment of cellular immunity [71]. The mean annual incidence of cryptococcosis in the general population in Colombia was 2.4 cases per 106 people between 1995 and 2010; in the population with human immunodeficiency virus (HIV), the incidence ranged between 3 and 3.3 cases per 103 people. [39].

Global literature has described fewer cases in children than adults [74], including those occurring in immunocompromised patients. The prevalence of *Cryptococcus* spp. in children with AIDS is estimated at 1 % and in adults about 6–8 % [75]. The low frequency of cryptococcosis in children cannot be explained by lack of exposure to the disease; in fact, one study shows that the majority of children older than 2 years of age have serological evidence of infection by *C. neoformans* [73].

The clinical diagnosis of cryptococcemia is difficult as clinical signs vary greatly due to infection in different organs [76]. Previous studies have shown that patients with cryptococcemia have a high fever; then, fever with tremors and chills in immunocompromised patients may be a warning sign for suspecting cryptococcemia [77]. Meningitis and meningoencephalitis are the most common clinical manifestations [78].

Usually, cryptococcosis diagnosis is made by mycological examination of cerebrospinal fluid (CSF), tissue biopsy, sputum, or other body fluids [79]. Approximately 80 % of AIDS patients and 50 % of non-AIDS have fungus observed in direct examination [70]. *Cryptococcus* spp. isolation from the bloodstream is not rare, but few clinical/epidemiological studies have examined its role and the underlying etiological agents. Previous studies reported blood culture as an important diagnostic method for cryptococcosis in AIDS patients [76, 80]. The ideal treatment is amphotericin B associated with 5-fluorocytosin. It is necessary to control CSF samples to certify the eradication of *Cryptococcus* spp. [81, 82]. A sterile culture within 2 weeks of starting treatment confirms the fungicidal action of drugs, and this is associated with therapeutic success [83].

We evaluated two articles on cryptococcosis, one in Colombia, descriptive, with a prevalence of 2.6 % in patients under 16 years old [39] and the other in Uruguay, series of cases, with patients in the range of 7–13 years [38] (Appendix 3). Only the descriptive study cited risk factors, with HIV infection at the top (24.4 %), followed by 7.3 % of autoimmune diseases, steroid use, and hematological disease, and 2.3 % of kidney disease, solid tumor, and prematurity [39]. The most frequent clinical manifestations were headache (78.1 %), fever (68.8 %), nausea and vomiting (65.6 %), confusion (50 %), and meningeal signs (37.5 %); the most frequent clinical presentations were meningitis, followed by disseminated cryptococcosis [38, 39]. Direct examination was the most used test for diagnosis, and capsular antigen detection was positive in all the cases that it was done, in serum and in CSF. Culture was positive in 89.5 %, with *C. neoformans* the most found (94.1 %) [38, 39]. The drug of choice was amphotericin B (93.5 %), with fluconazole as maintenance treatment [38, 39]. Recommendation for antifungal therapy in children with cryptococcosis is described in Table 4.

Mold infections

Mold infections must be cited because of their importance in immunocompromised patients. In this population, fungi are responsible for most deaths from infections. The overall risk of death in patients with mold infections can reach 30–70 % [84]. Early diagnosis of invasive mold infections and prompt implementation of aggressive antifungal treatment have proven to be critical for patient survival. A major advancement in

the approach for IFD in immunocompromised patients has been the international consensus definition for IFD published by the European Organization for Research and Treatment of Cancer Classification (EORTC), together with the acceptance of nonculture diagnostic techniques such as galactomannan (GM) and the accessibility to more safe and efficient antifungal therapies [85].

There are two prospective epidemiological studies published in children in LA from Chile and from Brazil in 2013. These studies evaluated the rate of IFD in children with cancer (Chile) and in children and adults with acute myeloide leukemia (AML) or myelodysplasia (MD) and underwent HSCT (Brazil). In the first, the authors aimed to identify risk factors for IFD in children with cancer, fever, and neutropenia in a prospective, multicenter study. A diagnosis of proven, probable, and possible IFD was made after episode resolution based on EORTC definitions. IFD was diagnosed in 35/604 febrile neutropenic episodes evaluated (5.8 %), of which 7 (1.2 %) were proven, 10 (1.6 %) probable, and 18 (3.0 %) possible; the authors did not mention any antifungal prophylaxis in the study. Most frequent mycosis in this population was candidiasis, followed by mold infections: invasive aspergillosis (IA) and zygomycoses [45]. In the second study, the authors observed a higher incidence of fusariosis in allogeneic HCT cohort (5.2 %) followed by IA and candidiasis. In study which includes mainly adult population more than 70 % were receiving antifungal prophylaxis with fluconazole [42].

Aspergillus spp. are ubiquitous fungi consistently documented as some of the most prevalent airborne molds. Conidia of *Aspergillus* species are often found in fireproofing or building material and are dispersed by ventilation systems into indoor air, including air within hospitals [44]. Infection is usually initiated by inhalation of airborne conidia and can cause a spectrum of clinical syndromes in the lung like IA, the most common in immunocompromised patient particularly those with prolonged and severe neutropenia due to cancer chemotherapy, high-dose corticosteroids, or broad-spectrum antibiotics [86].

Some aspects of IA care appear to be the same for adults and children, but there are important basic epidemiologic, pathophysiologic, and treatment differences in IA in children and adults. Unfortunately, only a few small studies of aspergillosis in children have been reported in literature [84, 86–91], none performed in LA. As shown by adult studies, pulmonary IA is the clinical site most commonly identified [84, 86]. The cutaneous presentation of aspergillosis appears to be more common in children, from 13.7 % (19/139 patients) in a study published by Burgos in 2008 to 20 % (13/66 patients) in St Jude review and 41 % (16/39 patients) in Toronto study [84, 86, 87].

Early diagnosis is important to patient outcome, and the clinician should have a high index of suspicion, especially in patients with underlying malignancies who are neutropenic with a prolonged fever despite systemic antimicrobial therapy. Numerous diagnostic approaches should be utilized. Computed tomography (CT) chest is more sensitive and specific than traditional chest radiographs in neutropenic patients and is considered the best method of diagnosis for invasive pulmonary aspergillosis. Nevertheless, it is important to note that the incidence of classic radiological findings is lower in pediatric patients than in adults; central cavitation of small nodules was not so frequent in pediatric series [84]. Other tools like galactomanan index (GMI) are useful for early diagnosis and became positive before the images. The specificity of the test may be lower in pediatric than adult patients [92] and further validation of the GMI for the early diagnosis of IA in high-risk pediatric patients is warranted. The recommend treatment by IDSA is voriconazole (evidence AI) as the same for adult [93]. Recommendation for antifungal therapy in children with aspergillosis is described in Table 5.

Fusarium is a genus of widely distributed saprophytic molds capable of causing disease in plants, animals, and humans [94]. Invasive fusariosis is uncommon and predominately affects immunocompromised hosts, particularly those with underlying hematological malignancy, neutropenia, and

Table 5 Recommendations for management on invasive aspergillosis in pediatric patients adapted from Groll AH, 2014

Drug		Dosage	Duration
First line	Voriconazole (AI)	Children aged 2–12 or 12–14 years old and weighing <50 kg: IV: (day 1): 8 mg/kg twice daily and after 9 mg/kg twice daily or PO: 9 mg/kg twice daily	6 to 12 weeks
		Children aged ≥ 14years old or 12–14 years old weighing ≥ 50 kg: IV: (day 1): 4 mg/kg twice daily and after 6 mg/kg twice daily or PO: 200 mg twice daily orally plus TDM	
	L-AmB (B-I)	3 mg/kg/day (IV)—once a day	
	Lipidic complex AmB (B-II)	5 mg/day (IV) once a day	

Source: [93]

IV intravenously, *PO* orally, *TDM* therapeutic drug monitoring

glucocorticoid exposure [95]. Although fusariosis is frequent in Brazil and associated with a very high mortality rate, to our knowledge, the literature in pediatric patients is scarce and there is no other data from children in LA.

Conclusions

IFD are important causes of morbidity and mortality. The knowledge of the incidence and prevalence in some regions is very important as geographic differences can interfere in the epidemiology of the species. Limited data in pediatric setting is available in South America. *Candida albicans* remains as the most frequent species of yeast isolated from bloodstream infections, but over the years, the numbers of candidemias caused by non-*albicans* species has been increasing. *C. parapsilosis* is more prevalent in younger children. PCM is an important mycose especially in Brazil with high rate of mortality and must be considered in endemic areas. Cryptococcis occurred in association with HIV infection, and the CNS clinical presentation is the most common. Other mold infection like *Aspergillus* spp., *Fusarium* spp., and zygomycosis must be considered especially in imunocompromised patients. More clinical studies must be done in pediatrics regarding to epidemiology, risk factors, diagnosis, prevention, therapy, and prognosis.

Compliance with Ethical Standards

Conflict of Interest Fabianne Carlesse, Adriana Maria Paixão de Sousa da Silva, and Maria Elena Santolaya declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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