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PEDIATRIC FUNGAL INFECTIONS (D CORZO-LEON, SECTION EDITOR)

AIDS-Related Mycoses in the Paediatric Population

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Abstract

Purpose of Review Fungal infections account for significant morbidity and mortality in HIV-infected children particularly in developing countries where there is lack of skilled personnel and infrastructure to make the appropriate diagnosis. This is further compounded by poor availability and accessibility of the antifungals needed to treat these infections. The purpose of this review is to highlight the paucity of data on AIDS-related mycoses in the paediatric age group and make appropriate recommendations to address challenges associated with mycoses in this population.

Recent Findings These infections are categorised in two broad groups in this population: mucocutaneous, which commonly affects nutrition and adherence to therapy and invasive fungal infections which are life-threatening. A literature search revealed a total of 29 published literatures across all AIDS-related mycoses in the paediatric population.

Summary Research to determine the true burden of the problem and greater funding with implementation of a package of care that will result in substantial reductions in morbidity and mortality in relation to AIDS-related mycoses in children are needed. It is imperative that the programmatic optimal package of care for children with advanced HIV disease is designed and implemented.

Keywords Mycoses · Paediatric · Advanced HIV disease · HIV/AIDS · LMICs

Introduction

Advanced HIV disease (AHD) is one of the most current challenges in the HIV pandemic with the 'plateauing' of HIV-associated mortality [1•]. It is of utmost importance to address the package of care for this population thus reducing mortality rates and improving quality of life. At the recently concluded 10th International AIDS Society Conference (Mexico, 21–24 July 2019), advocacy was made for addressing AHD in the paediatric population. AHD in children is defined as $CD4^+$ of < 200 cells/mm^3 or stage 3/4 disease (WHO staging) in children over 5 years of age, while any HIV-infected child less than 5 years is regarded as AHD [2••].

Opportunistic fungal infections are a major cause of mortality in HIV/AIDS-infected patients globally. 'A historic failure to focus efforts on the IFIs that kill so many HIV-infected patients has led to fundamental flaws in the management of advanced HIV infection' [3]. A report by Brown et al. in 2014 suggested that as many people die from serious fungal infections as TB or malaria [3]. Interestingly, despite this huge burden and high mortality rates, these diseases remain understudied and underdiagnosed (especially in resource-limited settings) compared with other infectious diseases [3]. This is further compounded by the lack of skilled personnel and infrastructure to make this diagnosis in resource-limited settings where a significant proportion of the 'at risk' patients are. Also, there is poor availability and accessibility of existing drugs to treat these infections in these settings.

There are five fungal infections commonly associated with significant morbidity and mortality amongst patients with AHD, namely, oropharyngeal and oesophageal candidiasis, pneumocystis pneumonia, cryptococcal meningitis, talaromycosis and histoplasmosis. Other emerging infections

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in AHD include emergomycosis and chronic pulmonary aspergillosis which is a complication of lung damage in HIV patients with tuberculosis. An estimated 4% of adults with AHD develop aspergillosis and most cases occur in patients with CD4 less than 50 cells/mm^3 [4].

Mycoses in Children with Advanced HIV Disease

As with adults, AHD is increasingly becoming challenging as 'children are re-presenting to health facilities with advanced HIV after a period of having interrupted their ART or while taking an ART regimen that is no longer effective due to development of drug resistance' [5••].

Fungal infections in paediatric AIDS-infected patients cause life-threatening infections and are often associated with excessive morbidity and mortality [6, 7]. Diagnosis of fungal infections in immunosuppressed children is often difficult because it presents with non-specific signs and symptoms. A high index of suspicion is therefore highly needed in immunosuppressed patients especially in those with persistent fever and neutropenia who fail to respond to appropriate broad spectrum antibacterial agents and in whom bacterial and viral infections have been excluded [8, 9]. The challenges of making a timely diagnosis of AIDS-related mycoses in the paediatric population are enormous and include lack of awareness especially in low-prevalence settings, non-specific clinical and radiological findings, difficulty in collecting clinical specimens and meeting the volume of sample required for good sensitivity, the need for anaesthesia to obtain a representative sample material using invasive procedures and to perform certain diagnostic procedures may be difficult to obtain in the paediatric setting, the fastidious and slow growing nature of fungal organisms, toxicity of antifungal drugs and insufficient robust data on usefulness of fungal biomarkers and molecular detection tests. Definitive diagnosis by tissue microscopy and culture-based methods has low yield, and is often difficult in the early stages of the infection [8, 9]. Fungal infections encountered in children with advanced HIV infection include *Pneumocystis jirovecii* pneumonia (PJP), cryptococcosis, histoplasmosis and talaromycosis. PCP, tuberculosis and severe bacterial infections constitute the major causes of mortality and morbidity amongst children with AHD, while cryptococcal disease is relatively rare [1•, 2••].

Oesophageal and Oropharyngeal Candidiasis

Candida infection is one of the most common fungal infections occurring amongst HIV-infected children. Oral thrush and diaper dermatitis have been reported in 50–85% of HIV-infected children [10]. Candida albicans is the most common cause of mucosal and oesophageal candidiasis in this group [11]. Candidal esophagitis is reported as the AIDS-defining condition in approximately 12–16% of children aged < 13 years in the USA, and continues to be seen in the post-HAART era amongst children who are not responding to therapy [10]. The associated factors are decreasing CD4$^+$ cell count (< 100/μL), high viral load and neutropenia (< 500/μL) [12–15]. Before the advent of HAART, concomitant oropharyngeal candidiasis (OPC) occurred in 94% of children with candidal esophagitis [11]. Children who develop oesophageal candidiasis despite being treated with HAART are less likely to have typical symptoms (e.g. odynophagia and retrosternal pain) or have concomitant OPC [13].

Disseminated candidiasis, though not common in HIV-infected children, has been reported in patients with HSV or CMV co-infection [13, 16]. Candidaemia has been reported in 12% of HIV-infected children with chronically indwelling central venous catheters for total parental nutrition or intravenous antibiotics [14, 17] and about 50% of the isolates were non-C. albicans spp. [14].

Pneumocystis Pneumonia

PCP is a leading cause of mortality amongst hospitalised children (29%) living with HIV [5••]. However, the lack of appropriate diagnostic facilities is a huge limitation to the determination of its global burden especially in resource-limited settings [5••, 6]. Pneumocystis pneumonia (PCP) is caused by the fungus *Pneumocystis jirovecii*. PCP is an important cause of pneumonia in the HIV-infected population and has been documented to account for 10% of death in post-mortem studies [18]. Another study revealed a high TB co-infection in this group [19]. In the African continent, it was previously assumed to be uncommon in the HIV population [20–23]. Early studies from Uganda and Zambia documented no *Pneumocystis* amongst HIV-infected patients [20, 24]. A South African report gave a similar finding of 1 (0.6%) positive sample out of 181 patients sampled for PCP [25]. However, in the same period, incidence of 3.6 to 11% was documented in Tanzania, Congo and Ivory Coast [21, 26–28]. These low rates are explained by lack of diagnostic support (both equipment and expertise) and due to a high mortality in these patients from more virulent pathogens and poor access to antiretroviral therapy (ART). However with better diagnostic methods and increasing access to ART, a study from Zimbabwe gave a PCP prevalence of 33% from 64-smear negative TB patients, using methenamine silver staining on bronchoalveolar lavage (BAL) samples (AFB) [29].

The picture in paediatric HIV-infected patients is similar. At the start of the HIV/AIDS pandemic, the incidence of PCP was 1.3 cases per 100 child-years from early childhood to adolescence and went up to 9.5 cases per 100 child-years in

infancy [30, 31]. Post-mortem studies of lung tissues from children with AIDS revealed an incidence of 67% in Zimbabwe [32], 31% in children less than 15 months from Ivory Coast [33] and 48% in HIV-infected children under 12 months in Botswana [34]. PCP appears to occur early amongst HIV-infected infants (median age, approximately 13 months), suggesting that exposure to *Pneumocystis* is relatively extensive. One of the challenges with diagnosis in infancy is that the child's HIV status is usually undetermined at the period of highest incidence which has been shown to be 3–6 months of age [35]. Anti-*Pneumocystis* antibodies have been demonstrated in HIV-negative children in early years of childhood [36]. Following improvement of prenatal HIV testing and introduction of ART to prevent vertical spread, there have been significant decrease in paediatric HIV infection. However, a more recent study from Mozambique amongst children less than 5 years reported a prevalence of 6.8% [37].

The rate of PCP increases as gross domestic product (GDP) increases [38•]. A systematic review and meta-regression done by Lowe et al. with the aim of determining the predictors of PCP in tropical and low- and middle-income countries showed a strong positive correlation with per capita GDP. Countries with developed economy have reduced health risk due to their ability to combat the transmission of contagious diseases like tuberculosis caused by a highly pathogenic organism (*Mycobacterium tuberculosis*), while relatively non-pathogenic organisms like *Pneumocystis* becomes a greater threat. Improving diagnostics with economic development has also been hypothesised to increase the detection of PCP [38•].

Prevention is possible with oral co-trimoxazole and ARV therapy, but is not completely effective. UNAIDS and other agencies have articulated the target of zero AIDS deaths, not yet achieved. Deaths are falling but are not as fast as new HIV infections are falling. One of the more common causes of death is PCP. Autopsies done in Africa revealed PCP in 16% of children who died with HIV/AIDS during 1992 and 1993 [39••], in 29% of those who died during 1997 and 2000 [39••], and in 44% of those who died during 2000 and 2001 [39••]. A late presentation, missed opportunities for giving prophylaxis (i.e. cough attributed to TB or 'chest infection'), poor compliance and/or side effects, failing ARV therapy and probably co-trimoxazole resistance in *P. jirovecii* are all responsible for prophylaxis failures. Survival improves with earlier diagnosis [40].

An early diagnosis cannot be achieved without direct testing and detection of *P. jirovecii*. Additionally, atypical and mixed infection, patients require an accurate diagnosis. Possibly the strongest argument for testing suspicious cases is to rule out the diagnosis, so usually toxic high-dose co-trimoxazole can be avoided or stopped. This requires a highly sensitive assay which microscopy is not.

Detection of 1,3-beta-D-glucan (BDG) in serum has proved to be an excellent alternative test for PCP in the adult population. A meta-analysis of 12 studies in adults with possible PCP (717 patients were HIV positive, while 1724 patients where HIV negative) showed BDG assay to have a sensitivity of 96%, specificity of 84% and diagnostic odds ratio of 102.3, considerably superior to its performance for other invasive fungal infections [41]. However, none of these studies is done in children. The baseline values have been found to be slightly higher in children [42], and need further evaluation. In a recent pilot study to evaluate a molecular PCR–based test and serum 1,3-beta-D-glucan to determine the molecular epidemiology of infection as well as explore the possibility of using these assays as diagnostics in a high-risk cohort of paediatric HIV+ children, we enrolled a pilot sample of 20 HIV+ children from Nigeria presenting with symptoms of pneumonia and throat swabs were obtained using Zymo® transport media. These swabs were shipped to the Kolls lab (USA), and they were able to detect host hypoxanthine phosphoribosyltransferase (HPRT) or glyceraldehyde 3-phosphate dehydrogenase (GAPDH) RNA in each sample. Eight of these samples were positive for pneumocystis mtLSU rRNA by DNA PCR, and 4 were positive at the RNA level. Three patient samples also showed amplification of the serine protease (SP). However, they could not sequence this amplicon compared with the samples from Canada and the USA. We believe this may be due to genetic variation of *Pneumocystis* in Nigeria [43]. It is apparent that the genomics of *Pneumocystis* needs to be fully understood. Other essential questions that need answers are the following: What is the true epidemiology of the disease in the general population and in the HIV-infected population? What is the vector biology of this disease? What is diagnostics? Serology? Molecular? Can a point of care (POC) molecular diagnostic test be developed? Can this test use a non-invasive sample?

Cryptococcosis

Most cases of cryptococcosis in HIV-infected patients are caused by *Cryptococcus neoformans*. In contrast to adults, cryptococcal infections are very rare in children especially in children < 5 years of age [44•]. A retrospective review of paediatric HIV patients with cryptococcosis at a tertiary hospital in Cape Town, South Africa, over a 7-year duration identified only 7 children, with cryptococcal disease amongst whom the median age of cryptococcal diagnosis was 9.3 years (ranging from 6 to 13.6 years) [44•]. Also, in a laboratory-based survey performed in South Africa, the incidence of cryptococcal disease was estimated at 47 and 120 cases per 100,000 persons for HIV-infected children and adults, respectively [45]. In Nigeria, a recent report by Anígilájé et al. from central Nigeria to determine the prevalence and risk factors of

cryptococcosis amongst a cohort of consecutive HIV-infected children (≤ 15 years of age) with a CD4 count of ≤ 200 cells/mm^3 showed no cryptococcal antigenaemia (0%) amongst the 88 children tested [46]. Care should be taken in interpreting this result considering a recent report from the same country revealed geographical variations in CrAg positive rates across the country [47]. The theory of asymptomatic cryptococcal antigenaemia as a forerunner to symptomatic meningitis and death has been conclusively proven [48]. Thus, cryptococcal antigenaemia screening coupled with pre-emptive antifungal therapy has been demonstrated as a cost-effective strategy with survival benefit and has been incorporated into HIV national guidelines in several countries. However, this is yet to be implemented in a number of other high HIV burden countries; the question is whether the advanced HIV disease population also needs routine screening especially given the low cost of the test and the benefit of the screening. This question is particularly important in known high-burden cryptococcal antigenaemia countries such as South Africa and Nigeria [49]. It is also imperative that the 'environmental niche' of the causative organism (Cryptococcus spp.) is determined and preventive measures for exposure are examined. The essence is to prevent HIV-related deaths.

Histoplasmosis

Histoplasmosis is still widely misdiagnosed as multidrug-resistant tuberculosis, leading to numerous preventable deaths [50]. Most AIDS patients with histoplasmosis require a high dose of antifungal agents. Histoplasmosis is mainly transmitted by inhalation of microconidia of *Histoplasma capsulatum*; however, cases of transplacental transmission have been reported in pregnant women with histoplasmosis [51]. Clinical manifestations of histoplasmosis vary within the paediatric age group. The acute progressive disseminated (PDH) form

Table 1 Reported cases of AIDS-related mycoses in the paediatric age group

S/no.	Country	Type of disease and causative agent	HIV status	Reference
Pneumocystis jirovecii pneumonia				
1	Mozambique	*Pneumocystis jirovecii* (57 cases)	Positive	Lanaspa et al. [37]
2	Botswana	*Pneumocystis jirovecii* (15 cases)	positive	Ansari et al. [34]
3	Malawi	*Pneumocystis jirovecii* (16 cases)	Positive	Graham et al. [58]
4	South Africa	*Pneumocystis jirovecii* (88 cases)	Positive	Hurtado et al. [59]
5	Brazil	*Pneumocystis jirovecii* (7 cases)	Positive	Severo et al. [60]
6	Brazil	*Pneumocystis jirovecii* (6 cases)	Positive	Severo et al. [60]
7	Vellore	*Pneumocystis jirovecii* (2 cases)	Positive	Cherian et al. [61]
8	Indonesia	*Pneumocystis jirovecii* (2 cases)	Positive	Liauw et al. [62]
9	South Africa	*Pneumocystis jirovecii* (15 cases)	Positive	Fattia et al. [63]
Cryptococcosis				
1	South Africa	*Cryptococcus gattii* (361 cases)*	Positive	Meiring et al. [44]
2	New York	*Cryptococcal neoformans* (30 cases)	Positive	Abadi et al. [64]
3	Brazil	*Cryptococcus gattii/C. neoformans* (7 cases)	Positive	Severo et al. [60]
4	Colombia	41 cases	Positive	Lizarazo et al. [65]
5	USA	4 cases	Positive	Gonzalez et al. [66]
6	USA	9 cases	Positive	Leggiadroet al. [67]
7	Thailand	7 cases	Positive	Likasitwattanakul et al. [68]
8	USA	10 cases	Positive	Joshi et al. [69]
Histoplasmosis				
1	Colombia	4 cases	Positive	L´opez LF et al. [51]
2	Tanzania (Moshi)	Histoplasmosis in a child; serology	Positive	Crump JA et al. [70]
3	South Africa	Cutaneous and subcutaneous abscesses in child; *Histoplasma duboisii*	Positive	Mosam et al. [71]
4	South Africa	Disseminated histoplasmosis in a child; *Histoplasma capsulatum*	Positive	Pillay et al. [52]
5	Kenya	Disseminated histoplasmosis in 2 children; *Histoplasma capsulatum*	Positive	Pamnani et al. [72]
6	USA (Providence)	Congenital histoplasmosis; *Histoplasma capsulatum*	Positive	Alverson et al. [73]
Talaromycosis				
1	Thailand	*Talaromyces marneffei* (21 cases)	Positive	Sirisanthana et al. [56]
Coccidioidomycosis				
1	USA (Arizona)	*Coccidioides immitis* (1 case)	Positive	Connelly and Zerella [74]
Candidiasis				
1	USA	Candida albicans (36 cases), Esophageal candidiasis	Positive	Chiou et al. [13]
2	Zimbabwe	C. albicans (9 cases), disseminated candidiasis	Positive	Leibovitz et al. [16]
3	USA	C. albicans (52 cases), oropharyngeal candidiasis	Positive	Gona et al. [12]
4	USA	Non-albicans Candida spp. (27 cases), candidaemia	Positive	Walsh et al. [14]

*2% of studied population

predominates in infants approximately 80% [52], it is the most frequent clinical manifestation of histoplasmosis in HIV-infected children and often fatal if untreated. Few cases of PDH complicating AIDS in children have been reported [53]. In pre-schoolers, the most common clinical form is acute pulmonary illness, while the most frequently observed clinical presentation in school children and older children is the sub-acute form [52]. A Colombian retrospective study of paediatric patients done by Lopez et al. from 1984 to 2010 identified a total of 45 paediatric cases of histoplasmosis with 15% of these patients living with AIDS [52]. A review article on histoplasmosis in Africa also revealed 37 paediatric cases; 7 of them were HIV positive [53].

It is imperative that the true burden of this disease condition be determined. Thankfully, WHO has just included histoplasma urinary antigen into the essential diagnostic test list (https://www.who.int/medical_devices/diagnostics/selection_in-vitro/selection_in-vitro-meetings/sub-id-40-5/en/).

Talaromycosis

Talaromycosis (formerly known as penicilliosis), caused by *Talaromyces marneffei*, is a life-threatening mycosis in people living with HIV/AIDS and a major cause of HIV-associated mortality, especially amongst individuals with a CD4 cell count < 100 cells/mm^3 [2, 55]. It accounts for 4 to 15% of HIV-related hospital admissions in endemic areas (South East Asia and China) [56]. Talaromycosis is an AIDS-defining illness. Disseminated infection is usually fatal, with mortality rates of up to 30% [2]. Sirisanthana et al. reported a series of 21 HIV-infected children with disseminated talaromycosis infection in Northern Thailand with a very high mortality [57]. Other cases have been reported in the paediatric population but in HIV-negative children [2, 55, 58]. Table 1 details most of the documented reports/studies on AIDS-related mycoses in the paediatric population since the advent of the HIV pandemic, when compared with the reports from the adult population, there is a paucity of data.

Other Mycoses

Coccidiomycosis, though not an AIDS-defining infection, is endemic in the Southwest (mainly California, Arizona, and Texas), Mexico, and Central and South America [74, 75]. Children with HIV infection are at increased risk for infection with *Coccidioides immitis* in areas where coccidioidomycosis is endemic. The primary infection of the newborn occurs rarely. However, the infection of the genital tract of the mother can result in placental involvement, coccidioidal endometritis, and aspiration of infected amniotic fluid by the foetus [76]. Both in utero and perinatal transmission of *Coccidioides immitis* have been reported [76]. A report by Connelly and Zerella (2000) revealed one case of coccidiomycosis in an HIV-infected child from Arizona [78].

Sporotrichosis is an endemic mycosis caused by the dimorphic fungus *Sporothrix schenckii* sensu lato with a mean incidence of 156 per 100,000 persons in children in Peru [79]. Possible risk factors are playing in crop fields and on dirty floors [79]. Cutaneous-disseminated, disseminated and pulmonary sporotrichosis are rare and occur in less than 10% of cases; however, in patients with AIDS, the prognosis is poor [80]. However, cases with invasive pulmonary sporotrichosis in HIV-infected children can be successfully treated with oral fluconazole as seen in a case report from Kinshasa in the Democratic Republic of the Congo [81].

Table 2 Challenges with mycoses in the paediatric advanced HIV disease population and example interventions for addressing them

Human resources
• Review of training curriculum to include instructions for serious fungal infections into existing programmes and training of healthcare professionals involved in management of HIV-infected children
• Laboratory personnel capacity building
• Incorporate fungal disease surveillance into existing programmes
Knowledge gaps
• Epidemiological studies are necessary to capture the burden of cryptococcosis, histoplasmosis, oral and oesophageal candidiasis and aspergillosis
• Studies to understand the geographical diversity of *Pneumocystis jirovecii* and assess if resistance is emerging
• Future studies to identify possible less invasive representative samples
• Generate studies that will guide policy development for managing these patients
Diagnostics
• Point of care test should be developed to mitigate challenges with power (electricity), infrastructure, 'turn around time', and lack of skilled personnel
• Tests that are affordable and do not require cold storage are suitable for resource-limited settings
Financing
• Provide coverage of fungal disease diagnostics in existing programmes
• Mobilise funding for more antifungal agents in existing programmes
Governance
• Organise advocacy groups that will drive political will to develop national policy for AIDS-related mycoses

Conclusion

Vast regions of the world including sub-Saharan Africa, Asia and South America do not have complete access to laboratory facilities equipped for the diagnosis of AIDS-related mycoses in HIV-infected children, thus making the true burden and impact of this infection under-recognised. A recent study by Falci and Pasculatto (2019) revealed only 9% of centres in Latin

America and the Caribbean have the potential to apply for the minimum standards in mycology, as determined by the European Confederation of Medical Mycology [81]; the picture would not be much different in Africa. For instance, when modern diagnostic methods were applied, unsuspected pneumocystis infection was found to be the cause of up to 7% of all severe pneumonia in children younger than 5 years (25.7% of whom were HIV-infected) in a hospital in southern Mozambique; a previous study had found very few cases [35]. While there has been a significant advance in diagnosis of cryptococcosis (with the development of the lateral flow devise), which has impacted the patients with advanced HIV disease even in developing nations, the same cannot be said for other life-threatening AIDS-related mycoses. Challenges with power generation (electricity) and lack of skilled personnel in resource-limited setting further buttresses the need for point of care diagnostics which are affordable in these settings. Our review has highlighted the knowledge gaps in this vulnerable population and proffered some short-term measures going forward (see Table 2).

Compliance with Ethical Standards

Conflict of Interest Bassey Ekeng, Omosalewa Olusoga and Rita Oladele declare no conflicts of interest relevant to this manuscript.

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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