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Epidemiology of Endemic Mycosis in Children

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Abstract

Purpose of the Review This review is aimed to overview clinical and epidemiological aspects, as well as the diagnosis and management of four endemic mycosis in children.

Recent Findings The studies available in the specialized literature concerning endemic mycosis in children are scarce and have great variation due to the characteristic heterogeneity of diseases.

Summary The clinical image of these diseases shows clear differences as well as their expression in immunocompromised patients. An understanding of the geographic range, typical manifestations, diagnostic methods, and treatment of the endemic mycoses is key in assessing patients presenting with atypical infections who may have traveled to endemic areas.

Keywords Endemic mycosis · Children · Sporotrichosis · Histoplasmosis · Coccidiodomycosis · Paracoccidiodomycosis

Introduction

Endemic mycoses are a group of infectious diseases that has a characteristic geographical distribution, which is defined by environmental and/or climatic aspects [1••]. This group includes to histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, and sporotrichosis, among others, which are caused by thermally dimorphic fungi with the ability to change between mycelial and yeast forms at different temperatures [2].

This review focuses on epidemiological, clinical, and targeted aspects of the diagnosis and treatment of four main endemic mycosis in children. Broadly, endemic mycoses can be divided into systemic endemic mycoses, which cause systemic infection after the inhalation of spores, and cutaneous endemic mycoses, which follow traumatic inoculation of the skin. Although the different diseases encompassed in endemic mycosis can cause disease in immunocompetent patients, there are several variations in epidemiology and clinical manifestations that motivate their individual study (Table 1). This includes the susceptibility to, and severity of infection in immunocompromised hosts [1••, 2, 3••, 4, 5].

Paracoccidioidomycosis

Paracoccidioidomycosis (PCM) is one of the most common endemic mycosis in Latin America; however, it does not represent a mandatory reporting disease, and thus, the actual impact on global public health is unknown. However, it has been estimated that the incidence in endemic areas varies from 3 to 4 new cases per million inhabitants. Recently, five cryptic species have been described as the main causes of PCM: *P. brasiliensis (ss)*, *P. lutzii*, *P. americana*, *P. restrepiensis*, and *P. venezuelensis*. PCM is characterized by presenting in rural tropical or subtropical climates in various countries of Latin America, including Mexico and Argentina; therefore, the disease is comprised between the Tropics of Cancer and Capricorn [6,7].

Pediatric cases comprise 5% of overall incidence [1••]. The most common form in children is the acute or subacute lymphoganglionar type, distinct from the adult population. In this group (adult patients) of patients, mucocutaneous presentation is the most common, followed by chronic pulmonary. When delayed diagnosis or inadequate treatment is made, the disease can develop into severe and lethal clinical forms with multisystem commitment involving organs of the

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Table 1 Characteristics of the main endemic mycosis in children

Disease	Sporotrichosis	Coccidiodomycosis	Histoplasmosis	Paracoccidiodomycosis
Etiologic agents	*S. schenckii (ss)* *S. brasiliensis* *S. globosa*	*C. immitis* *C. posadasii*	*H. capsulatum (ss)* *H. mississippiense* *H. ohiense* *H. suramericanum.*	*P. brasiliensis (ss)* *P. lutzii* *P. americana* *P. restrepiensis* *P. venezuelensis*
Rout of entry	Cutaneous (trauma) Exceptional respiratory	Respiratory Exceptional cutaneous	Respiratory Exceptional cutaneous	Respiratory Exceptional cutaneous
Geographic conditions	Tropical temperate climates	Dry desert climates	Tropical climates	Tropical climates
Clinical features	Cutaneous lymphangitic	Pneumonia Ganglionar cutaneous dissemination	Pneumonia Visceral dissemination	Pneumonia Cutaneous and mucosal dissemination
Differential clinical diagnosis	Non-tuberculous mycobacteria infection	Tuberculosis	Tuberculosis	Tuberculosis
Mycological elements -Parasitic form -Infectious form	Elongated yeast Sympudolic microconidia	Arthroconidia Spherules	Intracellular yeast Spiculated or digitiform conidia	Multigem yeasts Hyphae with chlamyconidia
Immunological tests	Intradermal reaction (sporotrichin)	Intradermal reaction (coccidiodin) Serology: complement fixation	Intradermal reaction (histoplasmin) Serology: complement fixation	Serology: Precipitins Complement fixation
Treatment	Itraconazole Potassium iodide Anfotericin B	Amphotericin B Itraconazole	Amphotericin B Itraconazole	Itraconazole TMP-SMX Amphotericin B

reticle-endothelial system, lungs, and digestive tract, with a 10–15% infant mortality rate [1••, 8].

PCM is not common in children, since most cases are reported in subjects over 30 years of age [9]. The main predisposing factors are age, alcoholism, smoking, and occupational exposure in agriculture. There is a predisposition to affect men (15:1), even though the paracoccidioidin skin test suggested a similar incidence in both gender. In addition to the above factors, the presence of estrogen inhibits the mycelium-yeast transition [10]. Among the pediatric population, there is no increase in predisposition in relation to sex, and the most common age ranges between 3 and 9 years of age [11]. Most PCM cases (about 80%) are reported in Brazil, followed by Colombia, Venezuela [12–14] although the disease spreads from Mexico to Argentina, involving sites with humid climates, predominantly in tropical and subtropical areas [15–18].

PCM clinical presentation in the pediatric population is acute or subacute and it is called "juvenile" form, in adults chronic clinical forms predominate. In children, PCM develops shortly after exposure, causing a severe and widespread disease [19, 20]. The development of the disease involves the reticuloendothelial system, presenting a mononucleosis-like syndrome as well as hepatomegaly and splenomegaly. In the pediatric population, the spread of the infectious process occurs in up to 70% of cases, while in adults, spread is rarely seen. This spread of infection is associated to a decreased Th1 response, leading to an anergic clinical form; it manifests with deterioration of the general condition, fever and polyadenopathies [21–23]. The most common laboratory findings are anemia, leukocytosis, severe eosinophilia, accelerated erythro-sedimentation, and hypergamma-globulinemia [24]. Diagnostic approaches are performed by detecting and identifying the fungus in sputum samples, obtained by bronchio-alveolar lavage; samples obtained from cerebrospinal fluid, or bone marrow biopsy, are useful in disseminated cases. Culture has a sensitivity of 90%; fungus is slow growing (it takes 20–40 days) and grows at 37 °C to convert the mycelial phase to yeast form [11] (Fig. 1 (1A, B)). Serological tests support diagnosis and evaluate the response to treatment. Protein chain reaction (PCR) test is also useful [25, 26]. Double immunodiffusion and contraimmunoelectrophoresis offer sensitivity ranges between 80 and 97% [27]. The ELISA test exhibits high sensitivity (80%) in cases of histoplasmosis during pre-treatment and during relapse (80% vs 65%, respectively) [28•]. Brazil is a region with a high incidence of PCM due to its climatic and geographical characteristics. A retrospective study carried out in Sao Paulo analyzed more than 1000 cases, 97% had positive serology by counterimmunoelectrophoresis, and 65% was confirmed by histopathological analysis and 23% by culture [12].

There are not enough studies to assess the effectiveness of the different treatments available to manage the disease [29]. Although azoles such as itraconazole have the same efficacy as sulfones, the first option is preferred for managing most mild to moderate forms, prolonged treatment is required with itraconazole (12 months minimum) [9]. Some authors

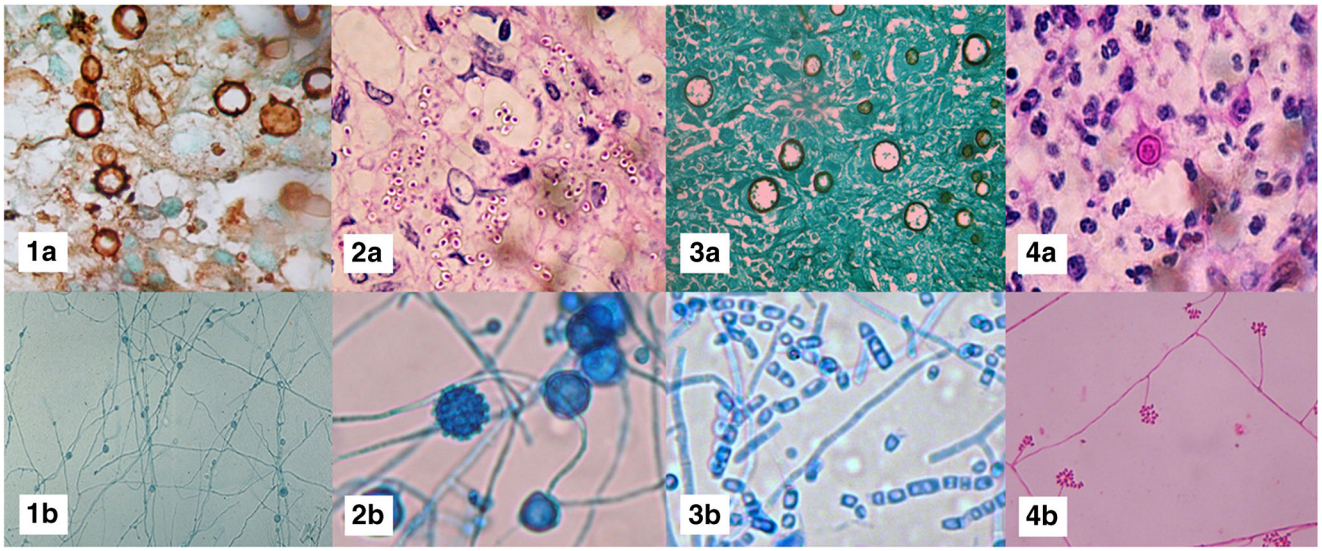

Fig. 1 (4) *Paracoccidiodes brasiliensis*: (1A) Multigenered yeasts (Grocott, × 40). (1B) Hyphae with clamidoconidia (Cotton-blue, × 40). (5) *Histoplasma capsulatum*: (2A) Intracellular yeasts (PAS, × 100). (2B) Spiculetad conidia. (7) *Coccidiodes immitis*. (3A) Multiple spherules (Grocott, × 40). (3B) Rexolytic arthroconidia (Cotton-blue, × 40). (8) *Sporothrix schenckii*: (4A) Asteroid body (PAS, × 40). (4B) Sympudolic microconidia (Erythrosine, × 40)

recommend sulfones such as trimethoprim sulfamethoxazole for 18–24 months in pediatric cases [30]. Amphotericin B deoxycholate is preferred for severe forms. Treatment protocols for pediatric cases are similar to those of adults [31]. Voriconazole is an effective option for moderate to severe cases [32], showing a profile of efficacy similar to itraconazole, so either of them can be used [33]. The duration of the schemes usually ranges from 6 to 24 months; this is based on disease severity and evolution [32]. Response to treatment is evaluated based on clinic, complementary tests and serology. The normalization of laboratory parameters could take long; eosinophilia, erythro-sedimentation, and hypergamma-globulinemia will be in normal ranges after up to 12 months of treatment [1••, 6, 32]. Persistence of infection should be considered when serological titers are maintained at high levels after 1 year of treatment. Although rare in the pediatric population, the diagnosis of PCM should be considered in patients from endemic areas who develop manifestations of febrile lymphoproliferative syndrome, anemia, hypereosinophilia, and hypergammaglobulinemia [1••].

Histoplasmosis

Histoplasmosis is a disease caused by cryptic species of *Histoplasma*: *H. capsulatum (ss)*, *H. mississippiense*, *H. ohiense*, and *H. suramericanum* [34]. Histoplasmosis is an opportunistic infection in subjects with acquired or iatrogenic, impaired cellular, and/or humoral immunity [35]. Pediatric cases of histoplasmosis have heterogeneous clinical forms; in infants, the most common clinical form is acute progressive dissemination, while in older children, the most common form is subacute. Histoplasmosis is usually self-limiting in immunocompetent children, while in immunocompromised children, the disease is more aggressive and disseminated. Studies on histoplasmosis in children are limited to isolated cases and small series of cases mainly from countries such as Brazil and Colombia, and less frequently from Panama, Costa Rica, Venezuela, and Ecuador [36].

Pediatric cases occur in approximately 5%, and in adolescents, it is higher. The disease occurs often in men than in women (1.5:1 ratio), and in ages between 6 and 9 years of age. Malnutrition has often been associated with histoplasmosis in children (37% of pediatric cases) and is considered the main predisposing factor and can contribute to poor disease prognosis. Another important aspect to consider is caloric protein malnutrition, which in children is one of the most important causes of immunosuppression, consequently generating poor immunological responses in histoplasmosis favoring aggressive forms of the disease [37].

Occupational exposure and severe acquired immunodeficiency such as AIDS are risk factors that can contribute not only to the presentation of the disease, but to the development of severe forms of histoplasmosis [38].

Histoplasma capsulatum (s.l.) usually penetrates through the airway by inhalation of microconidia; spores or conidia are easily transported and reach the alveolus, generating a primary complex similar to tuberculous, consisting of lymphangitis and hilar adenopathies [39•, 40]. The immune response against fungi appears in approximately 3 to 4 weeks; during first infection, subclinical spread, especially to lymph nodes and spleen, may occur. Once the primary event is

resolved, the majority infections (95%) will be spontaneously self-limited and only maintain immune memory response; calcified nodules are rarely seen in the lungs, spleen, and lymph nodes. Treatment is generally reserved for those with diffuse pulmonary infection with moderate to severe symptoms, progressive disseminated infection, or central nervous system infection [39•, 41].

In addition to lung disease, histoplasmosis in children can lead to involvement of the bone marrow, which is directly related to the host's immune status [42]. One manifestation of progressive disseminated histoplasmosis (PDH) is pancytopenia and in more aggressive cases, disseminated intravascular coagulopathy [43]. PDH can also involve the liver, spleen, adrenals, skin, gut, bone marrow, or central nervous system and is lethal if untreated [1••].

Pediatric cases usually occur with fever and cough in 74% and 57% of cases, respectively, although this finding varies according to the literature consulted [44, 45•]. The most severe clinical forms of the disease are seen in children under the age of 2, where progressive disseminated disease is present [46]. PDH affects the central nervous system in up to 48% of cases. The meningeal form develops nonspecific symptoms such as meningeal irritation and headache. The study protocol for these cases includes samples of cerebrospinal fluid for culture, serological, and/or molecular tests; detection of urinary antigen is also used [45•, 46].

Many cases of histoplasmosis with neurological symptoms can be confused with tuberculosis, due to the similarity of symptoms and findings in biochemical studies of cerebrospinal fluid (mononuclear pleocytosis with predominance of lymphocytes and increased protein contents), and delay the correct treatment when anti-tuberculous therapy is stated without any success, which can increase the mortality of these patients; other complications include neurological lesions caused by inadequate treatments [47]. In a previous study, it was observed that 15% of patients with histoplasmosis-associated meningitis and about 99% of non-bacterial meningitis had been diagnosed as tuberculosis [48]. In clinical practice, it is difficult to make a diagnosis pretreatment of fungal meningitis, allowing the progression of the disease with increased severity of the sequelae [1••, 46, 47].

Diagnosis of histoplasmosis in children depends on a high rate of suspicion based on factors including a pediatric malnutrition patient with fever, anorexia, headache, asthenia, and clinical data suggestive of meningeal irritation [46]. The most common radiographic abnormality are pulmonary infiltrates similar to those observed in tuberculosis. Radiographic findings in the lungs in patients with histoplasmosis are similar to those observed in patients with tuberculosis; fungal culture (Fig. 1 (2A, B)) allow a more accurate diagnosis [49], as well as antigenic tests and molecular studies, showing a more specific, reliable, and early diagnosis [50].

Amphotericin B for 1–2 weeks followed by itraconazole for a total of 12 weeks is recommended for severe acute pulmonary histoplasmosis [1••, 51]. A 4–6 weeks with amphotericin B is recommended in progressive disseminated histoplasmosis [52].

Coccidioidomycosis

Coccidioidomycosis is caused by cryptic species: *Coccidioides immitis*, *Coccidiodes posadasii*. The disease predominates in the southwestern United States, and some areas of Mexico and South America, mostly in arid areas [53]. Cases of coccidioidomycosis often do not produce symptoms and resolve spontaneously without treatment; however, some of them may develop severe lung condition and spread to bone, joints, skin, soft tissues, and/or central nervous system [54], even without affecting the lungs. Disseminated disease can be life-threatening [55]. Fisher et al [56], reported an increase in the need for hospitalization in cases of coccidioidomycosis in children. Although the disease has been extensively described in adults, there are few studies in the pediatric population. In a 2002 study, it was observed that about 40% of pediatric patients with coccidioidomycosis belonged to a non-endemic area, highlighting the benefit of reporting the disease in this age group [57].

According to one study, central nervous system infection can be seen in a third of cases with disseminated disease, pointing out the importance of conducting a targeted search in patients with suspected coccidioidomycosis, as well as in those with prior diagnosis of the disease [58].

Direct examination, culture and histologic examination, complemented by serology (anticoccidioidal antibodies) and complement fixation (titers ≥ 1:32 is associated with dissemination and titers ≥ 1:128 are linked to failure of medical therapy requiring surgical intervention in patients with bone disease), have been the pillars for the diagnosis of the disease [58, 59]. Supplemental qualifications may also reflect hospital stay time, disease severity, and surgical requirement, supporting the importance of aggressive, early antifungal [58].

Diagnosis of coccidioidomycosis in children is more complicated than in adults, mainly due to differences in immune system maturity. Different from what happens in immunocompetent adults, supplement titration is usually negative in children younger than 6 months of age. Culture and histopathological study remain the best options in this group of patients (Fig. 1 (3A, B)) [58].

Treatment is recommended for severe pulmonary infection, and extrapulmonary disease using fluconazole preceded by an initial course of amphotericin B in critically ill patients. The duration of treatment can range from 3 to 6 months in lung disease or even prolonged in cases of meningitis. Surgical intervention including drainage of abscesses, debridement, and

ventriculoperitoneal shunt placement is often required. Options for salvage therapy include voriconazole, posaconazole, and intrathecal amphotericin (for meningitis) [60, 61].

Sporotrichosis

Sporotrichosis is a common subcutaneous mycosis in South American countries, categorized as a neglected endemic disease, which cause chronic disease in any age group [62]. Sporotrichosis is caused mainly by three species: *Sporothrix schenckii (ss)*, *S. brasiliensis*, and *S. globosa*, a thermally dimorphic fungus. The highest incidence is in South American countries, particularly Brazil, Uruguay, and Peru; however, the disease is also frequent in Mexico, Japan, and India. Outbreaks in China, North America, South Africa, and Australia have also been documented [63]. Sporotrichosis affects children in certain areas of endemicity; it is rare in children of non-endemic countries. In a previous study, it was reported that 62% of cases of sporotrichosis were patients under 14 years of age [64•].

Pediatric sporotrichosis has not been sufficiently studied; risk and prognostic factors in this age group are little known [65–67].

Although pediatric cases have been reported in different countries (Brazil, Peru, Mexico, Venezuela, USA, and China), the global incidence of sporotrichosis in this age group is unknown. The frequency of pediatric cases is reported in one third of cases and only in hyper-endemic areas can reach half of the cases [66, 67].

Radical changes in the lifestyles of the population of endemic regions have changed the frequent disease, mainly in the pediatric population. The most common clinical form of sporotrichosis in pediatric patients is lymphocutaneous type compared to the fixed variant (proportion 2:1) [64•]. There has recently been an increase in the incidence of the disease in children between the ages of 5–9 and a decrease in younger children; most cases of sporotrichosis reported in children between 10–14 years of age mainly affects the face, this is probably due to the increased susceptibility in an area exposed to several traumatisms [65, 68, 69]. Sporotrichosis in children has been associated with traumatic inoculation with contaminated material (plant debris) and occasionally with animal transmission (cat and squirrels scratches, rat bites, including insect bites) [70].

Infection most commonly follows traumatic inoculation of the skin and subcutaneous tissue with contaminated soil, decaying vegetation, sphagnum moss, or hay. Zoonotic transmission from cats (Brazil) and armadillos (Uruguay) has been reported [62]. Children typically present with cutaneous disease of the face or limbs, either “fixed” with a single chronic ulcerative lesion or “lymphocutaneous” with multiple nodular lesions spreading proximally along the lymphatic vessels [64, 71].

The progressive increase in the number of cases of sporotrichosis in the pediatric population could be explained by the high diversity of causal agents (six genotypes of *S. schenckii* have been identified) or the increase in virulence in hyperendemic areas [71, 72]. The average duration of the disease is variable according to the region of origin, agent involved, patient age, immune status, etc. The average duration of the disease varies according to the region and can be about 1 to 2 months [64•], which could be explained by children’s difficulty expressing symptoms and parental care [64•65–68].

Osteoarticular disease is rarely seen, similarly to the previous mechanisms of infection; it is the result from direct inoculation or hematogenous spread. Pulmonary infection, meningitis, and disseminated disease are very uncommon, occurring primarily in hosts with impaired cellular immunity [64•, 65–71].

From a mycologic point of view, sporotrichosis is diagnosed with the isolation of *S. schenckii* (Fig. 1 (4A, B)). Histopathological analysis may have some additional findings like yeasts or asteroid bodies. Routinely skin test antigen may be helpful; however, it is not a commercially available standardized test [67, 70].

The drug of choice for sporotrichosis (lymphocutaneous and fixed) is itraconazole, 100 mg for 12 weeks, ranging from 2 to 64 weeks. However, potassium iodide has been extensively used with excellent results. In some countries (Mexico, Venezuela, and Brazil), it is the treatment of choice in children, due to the low cost and affordability [63, 64•, 73]. The safety and efficacy profile of potassium iodide are excellent even in low doses in children; however, the frequent adverse events limit its extensive use [73].

Initial therapy with amphotericin B is recommended in extracutaneous disease. Terbinafine and potassium iodide are potential alternatives where itraconazole is unavailable or contraindicated [63].

Conclusions

Diagnosis of endemic mycosis in children is a clinical challenge and requires a high rate of suspicion, mainly in patients who do not come from areas of high incidence. Endemic mycosis in children may have atypical clinical forms and in some cases, such as histoplasmosis, can confuse the clinician and delay effective treatment, worsening the prognosis. Progressive changes in environmental temperature, a product of global warming, as well as the ease of travel to endemic countries and the use of immunosuppressive drugs or the increase in immunosuppressive diseases, may contribute to an increase in the incidence of this group of diseases.

Compliance with Ethical Standards

Conflict of Interest Alexandro Bonifaz, Yessica Estrada-Caraveo and Andres Tirado-Sanchez 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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