

# Paracoccidioidomycosis in children and adolescents

## *Paracoccidioidomicose em crianças e adolescentes*

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### ABSTRACT

Paracoccidioidomycosis (PCM) is an important systemic mycosis; it is restricted to Latin America, and Brazil is the most affected country. Children and adolescents account for approximately 5 to 10% of all cases with the acute form of the disease, which afflicts the mononuclear phagocytic system, in particular, lymph nodes and abdominal organs. Involvement of bones and joints has been observed more often in these age groups in recent years. Extensive systemic involvement as well as ascites, jaundice, and malnutrition is associated with worse prognosis. Intestinal malabsorption is the most serious sequel in young patients. Treatment with antifungal medication must be maintained for 18 to 24 months, and rigorous clinical and laboratory monitoring should be performed even after the suspension of the specific treatment. Disease relapses are frequent, mostly due to short treatments. About 10% of children and adolescents with PCM evolve to death.

**Key words:** Paracoccidioidomycosis; Paracoccidioidomycosis/therapy; Antifungal Agents; Child; Adolescent.

### RESUMO

*Paracoccidioidomicose (PCM) é uma importante micose sistêmica, restrita à América Latina, sendo o Brasil o país mais afetado pela doença. Crianças e adolescentes representam cerca de 5 a 10% dos casos e cursam com a forma aguda da doença, que acomete o sistema fagocítico mononuclear, em especial linfonodos e órgãos abdominais. Acometimento de ossos e articulações tem sido observado mais frequentemente nessas faixas etárias nos últimos anos. Comprometimento sistêmico extenso, assim como ascite, icterícia e desnutrição, associa-se a pior prognóstico. A má-absorção intestinal é a mais grave seqüela da doença em jovens. O tratamento com antifúngico deve ser mantido por 18 a 24 meses e rigoroso monitoramento clínico e laboratorial deve ser realizado, mesmo após a suspensão do tratamento específico. Recaídas da doença são frequentes, principalmente devido ao tratamento por tempo curto. Cerca de 10% das crianças e adolescentes com PCM evoluem para óbito.*

*Palavras-chave:* Paracoccidioidomicose; Paracoccidioidomicose/terapia; Antifúngicos; Criança; Adolescente.

### INTRODUCTION

Paracoccidioidomycosis (PCM) is caused by the fungus *Paracoccidioides brasiliensis*, very prevalent in Brazil and responsible for about 50% of deaths resulting from systemic mycoses in the country.<sup>1</sup> It is the cause of sequelae and disabilities and is a health problem that has not received the due visibility.

In children and adolescents, PCM manifests itself often as a moderate or severe systemic disease, with relatively short evolution and death in about 10% of cases.

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The clinical picture is polymorphic, and the initial approach should consider the differential diagnosis of other important diseases such as lymphoma, leucosis, collagenosis, lymphatic and disseminated tuberculosis, histoplasmosis, and leishmaniasis. It is a chronic disease that requires treatment and prolonged medical care, which are often overlooked, leading to disease relapses with hospital readmissions and worsen prognosis. The initial disease staging and good monitoring care are influenced by the knowledge and medical experience caring for children with this mycosis in addition to the availability of diagnostic procedures. Over the past 10 years, it is observed that the search for health care has been earlier in these cases; however, ignorance about the disease is still the cause of delayed diagnosis and treatment. We emphasize the importance of PCM better understanding by pediatricians and the relevance of this article, which presents an epidemiological, clinical, diagnosis, and treatment approach for the disease focused on children and adolescents.

## EPIDEMIOLOGICAL AND PATHOGENIC ASPECTS

PCM in children was first described by Montenegro<sup>2</sup> in 1911. Children under 15 years old account for about 4-10% of reported cases.<sup>3-6</sup> The mycosis occurs very rarely in children under seven years of age, being described in patients over two years old, diagnosed mostly (65% of the time) in children over seven years of age and with similar distribution between males and females.<sup>3-5,7-12</sup> As cases of PCM in all age groups, most cases in childhood and adolescence are from endemic rural regions in Brasil.<sup>6-8,12</sup> Uncharacteristically, the disease in children living in cities and no history of attending rural areas has been documented.<sup>1</sup>

The main known infection route is by inhalation in places where the fungus was present, soil or vegetation. The inhaled fungal propagules form the primary lung complex in the infection, in an asymptomatic form, leaving a residual tumor that may contain the agent throughout the life of the host. In some cases, the infection progresses to symptomatic pulmonary disease and/or disseminated to other organs via the lymphatic system or hematogenic.<sup>4,13</sup> Placental infection has been documented in one single case.

However, there are no evidences of congenital transmission or infectiousness by the mycosis.<sup>6,13</sup> The occurrence of more than one case in a family has been rarely observed, and there have been no epidemic outbreaks.<sup>14</sup> The low prevalence and clinical diversity of the disease in children, with more acute and aggressive evolution than in adults, have been associated with less environmental exposure and immunological immaturity inherent in low chronological age. It is considered that the fungus virulence and host susceptibility, associated with poor socio-economic, health, and nutrition conditions, which are frequent in endemic regions, contribute to the development of the disease in some children.<sup>6,11,13</sup>

PCM in children and adolescents is manifested in the acute or subacute juvenile form, differing from the most common presentation of the disease, which is the chronic adult form, incident in adults over 30 years old. The disease is moderate or severe, with dissemination and parasitism. The estimated time between infection and onset of symptoms is relatively short, about months.<sup>4,13</sup> There is involvement of the mononuclear phagocyte system, particularly lymph nodes, and abdominal organs. Pulmonary and mucous membranes involvement is uncommon and, when present, occur in severe and advanced cases of the disease.<sup>3,4,7,8,10</sup> After suitable treatment and monitoring, scarring fibrosis may occur, setting sequelae with major function losses. Especially in children and adolescents, the disease that goes undiagnosed and untreated with a reasonable time evolves with broad systemic involvement and death in less than one year.<sup>8,13</sup>

## CLINICAL MANIFESTATIONS

The most common clinical manifestations of PCM in children and adolescents stem from infectious and inflammatory processes primarily involving lymph nodes, abdomen, intestines, abdominal organs, and bones and joints (Table 1). In principle, any organ or system may be affected by the mycosis. However, occasional locations such as eyes and male genitals were described in adults and very rarely in adolescents over 15 years of age.<sup>1</sup> General manifestations such as fever, ill-being, weight loss, and asthenia are reported in 40 to 80% of children with the mycosis.<sup>4,8,10,12</sup> The extent of symptoms is proportional to the degree of organic fungus dissemination.

**Table 1** - Manifestations of Paracoccidioidomycosis in children and adolescents

Manifestations	n (%)
Superficial lymph adenomegaly	90.0
Thoracic and/or abdominal lymph adenomegaly	35.0
Fever	80.0
Hepatomegaly	60.0
Splenomegaly	35.0
Malnutrition	35.0
Ascites	30.0
Abdominal mass	30.0
Jaundice	20.0
Esophageal varices and portal hypertension	<5.0
Obstruction, stenosis, compression and intestinal perforation	5.0
Diarrhea and/or intestinal bleeding and/or pain and abdominal bloating	20.0
Adrenal glands lesion*	<1.0
Bones and joints involvement	26.0
Skin lesions	35.0
Mucosar lesions	11.0
Radiological lung alterations	12.0
Central nervous system involvement (brain)*	<1.0

Data according to studies with 13 to 143 cases.<sup>3-5,7-10,12,15</sup>

\*Referred to one case, na autopsy finding.<sup>4</sup>

## Lymph nodes

Lymphadenopathy is the main manifestation of PCM in children and adolescents, and the lymphatic involvement is the indirect basis of other important organic and functional alterations, especially in the abdomen. The lymphadenopathy of more significant clinical expression is often located in the target ganglion chains or adjacent to sites of active infection. Superficial lymphadenopathy is observed in 90 to 100% of patients under 14 years of age, differing from the disease in adults, where it is reported in less than 50% of cases.<sup>3-5,7-10,12</sup> The research with lymphangiography shows the involvement of deep lymph vessels and lymph nodes in patients with the mycosis, including sequelae lymphedema after the scarring and healing phases.<sup>16</sup> The involvement of endothoracic lymph nodes is little observed radiologically.<sup>4</sup>

The most affected superficial lymphatic chains are the submandibular, anterior and posterior cervical, clavicular, and axillary. The lymphadenopathy may be of small, medium, or large dimensions, with palpable lymph nodes and often visible, hard, and painless (Figure 1). In large lymphadenopathy, lymph nodes are often fixed due to periadenitis, and tend to

float and form fistulas, draining a yellowish fungus rich content. Ganglia fusion may occur, forming large masses, simulating malignant neoplasias.



**Figure 1** - Girl at 10 years of age, residing in the countryside, with generalized lymphadenopathy, especially cervical, night fever and weight loss; two months of development and diagnosis of PCM by lymph node biopsy. She also presented periaortic lymphadenomegaly through abdominal ultrasound without visceromegaly. *P. brasiliensis* was detected in sputum, chest X-ray compatible with hilar lymphadenopathy and thorax tomography considered normal. The patient was treated with ketoconazole with good response; she is healthy, post-therapeutic monitoring for more than five years.

## Abdomen, intestines., and abdominal organs

Abdomen, digestive tract, and abdominal viscerae are commonly affected in children, adolescents, and young adults with PCM. While the involvement of mesenteric ganglia is common, gastrointestinal complications do not occur with the same frequency. Functional alterations can happen and compressions caused by lymphatic masses that cause crampy abdominal pain, sometimes mimicking acute surgical abdomen, in addition to prolonged diarrhea, dysentery, nausea, vomiting, constipation, and anal ulcers. Hepatomegaly, splenomegaly, and palpable masses are frequent and, eventually discrete abdominal alterations are observed only in complementary exams.<sup>4,7,8,15,17-19</sup>

The most affected intestinal segment is the jejunum-ileocecal region; duodenal involvement has been described in children, although it is considered occasional in PCM. The esophagus, stomach, and rectum involvement are also rare, being described in adults with the very advanced disease.<sup>18</sup> Nodular lesions secondary to hypertrophy of lymphoid formations in the intestinal submucosa lead to dilation, looping edema, and necrotic ulcers predisposing the enterorrhagia. The lymphoid hypertrophy and diffuse enteritis contribute to poor absorption of nutri-

ents and lymph extravasation into the peritoneal cavity and intestinal lumen. There is ascites formation and loss of fat, protein, lymphocytes, electrolytes, and other nutrients, along with feces, aggravated by frequent intestinal ulcerations, setting in a severe malnutrition state (Figure 2). Ulcers may progress to fibrosis and tumors that, together with mesenteric and hypertrophied retroperitoneal lymph nodes determine compressions, obstructions, and intestinal semi-obstructions. Thus, the severe malnutrition frames with electrolyte disturbance and dysproteinemia, of difficult control, may occur in either early stages of treatment and after a successful infection treatment.<sup>4,8,15,17-19</sup> Peritonitis resulting from intestinal perforations is a very serious complication in this mycosis in children and adolescents. Hypoalbuminemia, ascites, and jaundice are associated with poor prognosis and deaths by the disease.<sup>8,15,18-20</sup>



**Figure 2** - Female teenager, 12 years old, from rural areas, with fever, anemia, asthenia, generalized lymphadenopathy, large hepatosplenomegaly, and diagnosis of PCM, after extensive propaedeutic. With the specific treatment, she showed regression of symptoms during hospitalization for 45 days. Without a maintenance treatment and regular medical care, she was readmitted about 18 months later with a severe case of malnutrition, dyspnea, lung X-ray alterations, and broad abdominal involvement with visceromegaly, abdominal mass, and diarrhea. She progressed to multiple organ failure and death within 15 days in the ICU despite the specific treatment for the mycosis.

The liver is the viscerae most affected by PCM, often by compression of the biliary tract due to lymph adenomegaly.<sup>15,19</sup> The volume is increased by up to 60% of cases. However, large hepatomegaly occurs in less than 10%. Despite the parasitism, inflammation of bile ducts, granulomatous and fibrotic tissue lesions occurring in 50% of patients with mycosis, the liver function

is often preserved or slightly altered. Jaundice, when present, is mostly and commonly due to the compression of bile ducts and hepatic hilum. The great increase in transaminases and alkaline phosphatase are rare, and a usual slight increase of bilirubin occur, with a predominance of the direct fraction. Inflammatory processes and pancreatic bile duct obstruction are also described, however, without disturbance in the secretory function of pancreas.<sup>18-20</sup> Splenomegaly is reported in about 35% of cases. It is associated with congestion, hyperplasia, and hypertrophy of the Kupfer cells. Splenic calcifications and necrotic granulomatous lesions are described containing the fungus in the liver and spleen, however, portal hypertension and hematemesis rarely occur.<sup>8,9,12,19</sup>

The involvement of the adrenal glands with functional failure or hyperplasia, as described in the chronic form of PCM in adults, is not reported in children.<sup>21</sup> The adrenal disease in adults with this mycosis is common; there is a record of glandular lesions found in the necropsy of one child with this mycosis.<sup>4</sup> Thus, in the face of specific treatment options for adrenal insufficiency and prevention of the mechanism of death by Addisonian crisis, the investigation on the functional impairment of adrenal glands is justified in severe cases of the disease, in all age groups.

## Bones and Joints

The involvement of bones and joints by PCM has been increasingly reported in up to 35% of cases in the literature. First, it was reported in most patients in the fourth decade of life and pulmonary disease, i.e., with the chronic form of the disease.<sup>22</sup> In recent years, it has been reported more often in young patients with the acute mycosis form, particularly children, in about 20% of cases.<sup>1,3,4,8,12,23</sup> The involvement of bones and joints usually happens in the advanced systemic disease, however, it may be the only or the main form of disease presentation causing PCM to be included in the differential diagnosis of arthritis, especially in patients from endemic regions for this mycosis.<sup>24,25</sup> The lesions may be uni- or bilateral, and the major affected sites are the shoulder girdle, thorax, upper limbs, tibia, and iliac crest, regardless of age. The radiological aspect is of well-defined osteolytic lesions, in metaphyseal, epiphyseal, and diaphysis. The fungus may be isolated from the synovial fluid, affected joints, and bone marrow. In the latter, sig-

nificant eosinophilia in peripheral blood is often observed.<sup>25,26</sup> With treatment, lesions are replaced by fibrotic tissue and local bone formation. However, the initial staging of the disease should consider bone involvement, even in cases without specific symptoms, for the observation of care to prevent bone fractures and performance of serial radiographs in the monitoring process of healing.<sup>8</sup>

### Skin and mucous membranes

Skin lesions, common manifestations of PCM in adults, are uncommon in children; however, their occurrences are of importance because they usually occur in severe cases with the wide systemic spread of the disease. The skin lesions are more frequent than those in mucosae and are described in up to 45% of children and adolescents with this mycosis. They usually result from hematogenous dissemination of contiguous mucosal lesions, festering lymph nodes, foci of osteomyelitis, and surgical procedures such as biopsies.<sup>4,8,27</sup> In the early stages of the disease, papulo acneiform lesions varicella-like type can be detected, which may be confused with varicella.<sup>1,8,19</sup>

The mucosal lesions, considered the second most frequent manifestation in PCM in adults, rarely affect children.<sup>4,6,9,27</sup> However, some authors have reported most instances, including the classical form of mulberry stomatitis, in 30-40% of young people above 14 years of age with the acute form of the disease, and very disseminated.<sup>19</sup> The present authors observed mucosal lesions in 13% of cases in children and adolescents, located in the nose, eyelids, and oropharynx; contiguity with the adjacent skin is frequent, and disease is disseminated.<sup>8</sup> It is important to consider the differential diagnosis of mucocutaneous lesions of PCM with neoplastic lesions and other parasitic diseases, such as cutaneous leishmaniasis. Histopathological examination should be performed for a definitive diagnosis, especially in cases with ulcers in mucosae.<sup>1</sup>

### Lungs

Pulmonary clinical and radiological alterations of the mycosis in children occur in 3-10% of cases and are associated with important manifestations in other organs. Radiological findings are interstitial infiltrate, disseminated or localized nodules, pleural effusion,

and mediastinal, hilar, and tracheobronchial lymphadenopathy.<sup>3-5,7-10,12</sup> Hilar lymph node hypertrophy is the most frequent finding, observed in about 30% of cases.<sup>9,12,13</sup> Some authors believe that pulmonary involvement by mycosis in children may be more frequent, and emphasize the importance of thorax radiography in all cases of PCM.<sup>4,7</sup>

### Central nervous system

PCM in the central nervous system (CNS), neuro-paracoccidioidomycosis (NPC), is usually described in adults in the chronic disseminated form of the disease. More often, pseudotumoral granulomatous lesion in the parenchyma of cerebral hemispheres and symptoms of intracranial hypertension with motor, sensory, and cognitive deficits, headache, and convulsions occur. The meningeal form and other locations are infrequent; however, it is reported in 12.5% of PCM cases on average with children NPC references only found in autopsies.<sup>4,14</sup> However, a 10 years old boy, followed up by the authors, reason for a future publication of the case, presented the brain disease after 2.5 years of treatment while he was in post-therapeutic monitoring for PCM. He developed weakness in the lower limbs, tongue numbness, dyslalia, and brain injury. A new treatment with trimethoprim-sulfamethoxazole was applied with a good response. Thus, it is important to investigate NPC in children with this mycosis.

## DIAGNOSIS

### Fungus identification

The diagnosis is confirmed by the fungus presence in host tissues or secretions. The direct microscopy of scraped lesions, purulent secretion from lymph nodes or sputum, and biopsy tissue are used or isolated in culture, which can take weeks to months. The lymph node secretion is usually rich in cells that are characteristic of *Paracoccidioides brasiliensis*. The histopathology, less sensitive than isolation, may present false-positive results, confounding atypical forms of the PCM agent with other fungi.<sup>13</sup> The lymph node biopsy is particularly important in the diagnosis of the mycosis in children and adolescents, given the

aspects of the disease in this age group, with significant lymphadenopathy in most cases and reduced incidence of mucocutaneous and pulmonary manifestations compared to the disease in adults. The biopsy has been performed, for the purpose of diagnosis, in over 80% of cases.<sup>5,12</sup> The fragments of biopsied tissue should be preserved separately in sterile saline and formalin for the histopathologic and mycological examinations, respectively.

### Serological diagnosis

Patients with PCM produce specific antibodies that persist for a long time and are correlated directly with the severity of the disease. Thus, serology is very useful in the diagnosis and monitoring of cases. Species-specific antigens should be used for the detection of antibodies; the most widely used is the glycoprotein 43-kD (gp43). Among the various tests developed, the most routinely performed are double immunodiffusion (ID), enzyme immunoassay (ELISA), and Western blotting (WB). By employing standard techniques and suitable antigens, these tests show sensitivity between 85 and 100%.<sup>28</sup> ID is the most available test for PCM because it has a sensitivity of 90% and specificity of 99 to 100% in addition to being of easy execution and low cost. Performing more than one serological test increases diagnosis sensitivity.<sup>13</sup> Serology can be positive in healthy individuals living in endemic areas. Differences in culture media and cultivation time of strains used in the production of tests can lead to discrepant test results making comparisons difficult. Other limitations of serology tests are the cross-reactivity with other fungi and reduced sensitivity in immunocompromised patients due to low levels of circulating antibodies.<sup>13,28</sup>

The detection of the antigen can be very useful in the diagnosis of immunosuppressed patients, especially those with AIDS, in which the antibody response may fail. In children with the disseminated disease and adults with the multifocal form, antibodies may be undetectable because they are coupled with excess antigen or the patient's inability to raise antibodies. In such cases, the detection of circulating antigens not only allows an early diagnosis but also the monitoring of treatment response. There may be false-negative results due to antigen polymorphism, and false-positive due to some cross-reactivity with histoplasmosis or lobomycosis.<sup>13</sup>

### Molecular diagnoses

Molecular diagnoses by polymerase chain reaction (PCR) and other related techniques, is still limited to research laboratories. The method is essential to distinguish and identify circulating genotypes. It has demonstrated success in the detection of *P. brasiliensis* when there is a failure in isolation and blood levels of antigen or antibody are too low for an immune diagnosis. As the immune-histochemical technique with monoclonal or polyclonal *P. brasiliensis* antibodies, PCR is useful in cases of chronic disease and immunosuppressed patients where *P. brasiliensis* can also be found in minute forms and mistaken by dimorphism with other fungi, even with *Pneumocystis jiroveci*. However, it is emphasized that positive results by PCR not always correspond to the disease and may represent latent infection or colonization.<sup>1,13</sup>

### Complementary exams

Several complementary exams are useful in assessing the extent of involvement and evolution of the patient. The most commonly performed are full blood count, inflammatory activity markers, such as erythrocyte sedimentation rate (VHS) and C-reactive protein (PCR), and serum proteins, electrolytes, bilirubin, liver enzymes, alkaline phosphatase, and gamma glutamyl transferase. The dosage of fecal fat and imaging tests such as chest, abdomen, and bones X-ray, contrast radiography of intestines, abdominal ultrasound, and CT scan are also used.

A child or adolescent with PCM often presents normocytic and normochromic anemia, which regresses with treatment in weeks or months. The anemia may be microcytic and hypochromic, and in this case, ferruginous treatment is indicated. Light to intense leukocytosis, neutrophilia with left shift, and toxic granulations in severe cases are observed. Eosinophilia is quite frequent, and lymphocytopenia or lymphocytosis and monocyte may occur. The VHS and PCR are usually increased. In relation to serum proteins, the alterations are more pronounced in acute and disseminated cases of the disease, where hypoalbuminemia, and hypergammaglobulinemia, and especially immunoglobulin G are observed.<sup>5,8,12,17,29</sup> In such cases, especially in cases of significant intestinal involvement, fecal fat can be elevated and levels of serum electrolytes reduced. Bilirubin and liver enzymes, al-

kaline phosphatase, and gamma glutamyl transferase are generally high when there are extensive abdominal lymphadenopathy and large visceromegalies.<sup>8,17-20</sup>

In imaging studies of children and adolescents with PCM, abdominal and bone involvement are mainly observed. There may be alterations throughout the length of the small intestine, especially in the terminal ileum, with a malabsorptive pattern, a sign of extrinsic compression by the nodes' loops and localized areas of stenosis. In the large intestine, the possible loss of haustrations interspersed with stenosis and intestinal occlusion are observed.<sup>4,8,17,18</sup> Ascites, lymphadenopathy, hepatosplenomegaly, dilated bile ducts, nodules and spleen and ganglion calcifications are detected on abdominal ultrasound.<sup>8,18,19</sup> Lytic lesions without periosteal reaction may be registered in bones.<sup>23</sup> Pulmonary involvement, uncommon in children, has a bilateral interstitial infiltrate pattern in the mid third of lungs ("butterfly wings"), mediastinal lymph nodes hypertrophy, and pleural effusion.<sup>5,7</sup> Brain impairment, observed in TCC of adults, is presented as other granulomatous parenchymal lesions, sometimes calcified.<sup>14</sup> Hyper proteinorachie and pleocytosis may occur with a mononuclear predominance, or CSF alterations may not occur.

## TREATMENT

Cases with enhanced systemic involvement must be initially treated with amphotericin B at a dose of 0.5 to 1.0 mg/kg/day, not to exceed 25 mg/application for children, with a cumulative dose of 30 mg/kg. Sulfamethoxazole/trimethoprim (SMZ/TM), 30-40 mg/kg/day of sulfamethoxazole, at twice daily doses, can be used parenterally and constitutes an alternative to the use of amphotericin B. It is especially suitable in cases of mycosis in the CNS.<sup>14,28</sup> Children or adolescents with moderate disease may be treated from the start with itraconazole or SMZ/MT.

Itraconazole has the advantages of using a single daily dose and is associated with the low occurrence of relapses (3-5%) and fewer adverse effects compared to other azoles. Ketoconazole can replace itraconazole although it is associated with more adverse effects and drug interactions. Voriconazole has been shown to be as effective as itraconazole in the treatment of PCM in adults, but there are no studies on its use in children. Fluconazole and voriconazole penetrate the CNS well and allow switching from the intravenous to oral route.<sup>8,28,30</sup>

Because the clinical response to treatment depends on the intensity of involvement and cellular and humoral immune response in the patient, it is essential to associate nutritional support and treatment of other ailments. After clinical improvement, which usually occurs between three and six weeks, the sequential treatment can be performed with itraconazole, 5-10 mg/kg/day immediately after meals and without opening the capsule, or SMZ/TM, or even ketoconazole, 5-8 mg/kg/day. The use of azole derivatives should be monitored through the dosing of hepatic enzymes.<sup>8,28</sup>

## CRITERIA FOR HEALING AND MONITORING

Because this is a chronic, progressive disease, and the drugs available for treatment are fungistatic, the treatment is carried out in two phases: attack and maintenance. The time of each phase and total time of antifungal use are variable and depend on the clinical evolution of the patient and treatment regimen used. The attack phase concludes with the clinical remission of the disease, and the maintenance phase lasts for months or years. If clinical remission occurs between two and six months and itraconazole was used, the treatment time can be 12 to 18 months. Relapse with the use of SMZ/TM (10-15%) have been associated with poor adherence to treatment or short therapeutic course. Criteria to guide the transition from the attack to the maintenance and interruption phases of using an antifungal agent are based on clinical evaluations and laboratory nonspecific, mycological, radiological, and serological exams.<sup>28,29</sup>

Anemia, eosinophilia, bilirubin, and increased aminotransferase revert gradually from 1-2 weeks of specific treatment, normalizing in three to six months. Leukocytosis, hypergammaglobulinemia, and increased VHS reduce early with a successful treatment and normalize in up to 12 months of treatment; they are considered important parameters in the initial approach and sequential treatment monitoring.<sup>12,29</sup> Serial ID and ELISA titers decline with clinical improvement after 1-3 months of treatment.

For the serologic criteria of cure, which generally takes place at 10-12 months of specific treatment, a negative or stabilizing ID titrations equal to or less than 1:2, obtained in two serum samples with a six months interval in between, are necessary.<sup>28,29</sup> Clinical or laboratory alterations, particularly elevated

VHS and IgG immunoglobulin and/or increased serum titers can mean disease relapse and the case should be re-evaluated considering restarting with a new therapeutic regimen and emphasis on adherence and monitoring.

Persistent low serum titers for years or lifetime are observed in some patients. After about 24 months of treatment initiation, and patient remaining under the cure criteria, assessments at every six to 12 months for at least five years are recommended. Some patients may initially present titers below 1:4. In these cases, the serological criterion based on ID will have limited value in monitoring.<sup>28,29</sup> Recent studies evaluate the standardization of antigenemia and molecular biology techniques for the diagnosis and monitoring of treatment of this mycosis.

It was concluded that PCM is a chronic infectious disease that progresses systemically with the specific and reversible immunological involvement against the fungus. Therapeutic success depends on the use of antifungal antibiotics and supportive measures in the early stages of the disease for a prolonged period. Experiments with vaccines and immune modulators to antifungal agents are promising in reducing the treatment time and minimizing organic sequelae resulting from scar fibrosis that occur in some cases after infection healing.<sup>30</sup> In children and adolescents, it is noteworthy the importance of diagnosis and early treatment in the first months of symptoms because the involvement of organs and abdominal viscerae – by parasitemia, compressions, and inflammatory processes - is associated with poor prognosis and death from this mycosis.

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