

# Brazilian guidelines for the clinical management of paracoccidioidomycosis

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## Abstract

Paracoccidioidomycosis is a systemic fungal disease occurring in Latin America that is associated with rural environments and agricultural activities. However, the incidence and prevalence of paracoccidioidomycosis is underestimated because of the lack of compulsory notification. If paracoccidioidomycosis is not diagnosed and treated early and adequately, the endemic fungal infection could result in serious sequelae. While the *Paracoccidioides brasiliensis* (*P. brasiliensis*) complex has been known to be the causal agent of paracoccidioidomycosis, a new species, *Paracoccidioides lutzii* (*P. lutzii*), has been reported in Rondônia, where the disease has reached epidemic levels, and in the Central West and Pará. Accurate diagnoses and availability of antigens that are reactive with the patients' sera remain significant challenges. Therefore, the present guidelines aims to update the first Brazilian consensus on paracoccidioidomycosis by providing evidence-based recommendations for bedside patient management. This consensus summarizes etiological, ecoepidemiological, molecular epidemiological, and immunopathological data, with emphasis on clinical, microbiological, and serological diagnosis and management of clinical forms and sequelae, as well as in patients with comorbidities and immunosuppression. The consensus also includes discussion of outpatient treatments, severe disease forms, disease prevalence among special populations and resource-poor settings, a brief review of prevention and control measures, current challenges and recommendations.

**Keywords:** Paracoccidioidomycosis. Guidelines. Clinical management. Diagnosis. Treatment follow-up.

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## ETIOLOGY

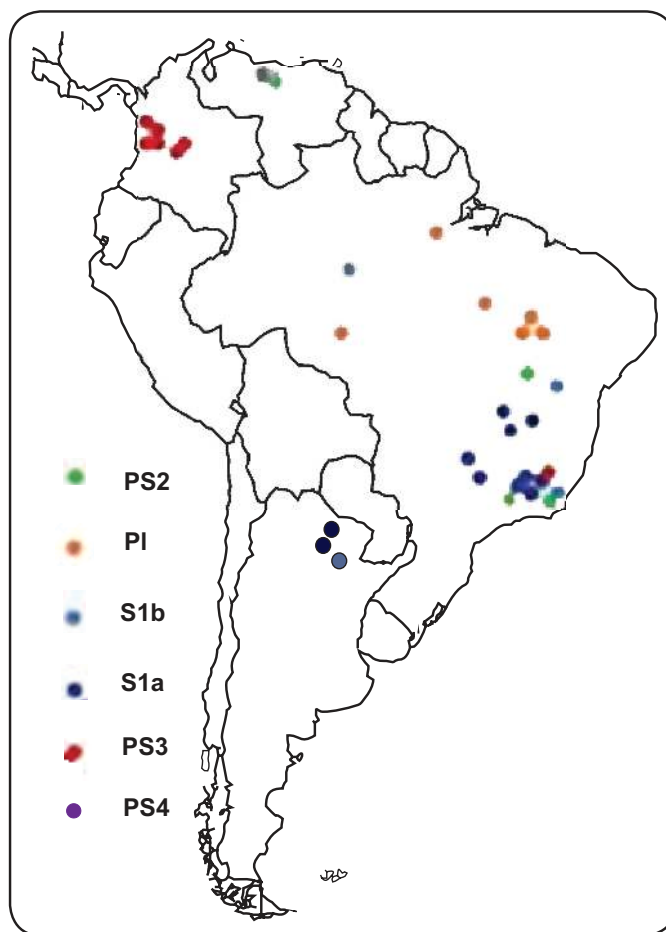
Paracoccidioidomycosis (PCM) is caused by thermophilic fungi that currently encompasses two species: *Paracoccidioides brasiliensis* (*P. brasiliensis*) and *Paracoccidioides lutzii* (*P. lutzii*)<sup>1</sup>. *P. brasiliensis* contains a complex of at least five phylogenetic clusters ranked as the following phylogenetic species: S1a, S1b, PS2, PS3, and PS4<sup>2,3,4</sup>. The phylogenetic species S1a and S1b are predominantly found in lower South America, especially in southeastern and southern Brazil, Argentina, and Paraguay. The PS2 species has a sporadic distribution and is less frequently reported, with human cases only being reported thus far in Venezuela and southeast Brazil (**Figure 1**). The PS3 and PS4 species are exclusively endemic to Colombia and Venezuela, respectively. *P. lutzii* encompasses a single species and is predominantly distributed in the Central West and Amazon regions of Brazil and Ecuador<sup>1,5,6,7,8</sup>. However, the real incidence of each phylogenetic species and its implication on clinical practice is difficult to establish because of the lack of guided studies comparing PCM forms and manifestations with their genetic background<sup>9</sup>. Radial immunodiffusion against the commonly used exoantigens containing a 43-kDa glycoprotein (gp43) suggests that *Paracoccidioides* spp. exhibit major antigenic variability. According to phylogenetic studies, different *Paracoccidioides* spp. isolates are distributed in different genotypes across multiple PCM endemic areas of Latin America. In particular, *Paracoccidioides* spp. in central Brazil (i.e. Mato Grosso and Rondônia) exhibit a lower rate of genetic similarity. Yet, *P. lutzii* isolates exhibit high species-specific antigen variability<sup>9</sup>, which has already been assessed in proteomic studies.

## ECOEPIDEMOLOGY

In nature, *P. brasiliensis* and *P. lutzii* develop as filamentous structures and produce infective propagules called conidia<sup>10,11</sup> (**Figure 2**). If inhaled, the propagules give rise to yeast forms of the fungus that become parasitic to the host. *Paracoccidioides* spp. can cause infection and disease in humans and domestic and wild animals, although only a few active disease cases have been observed in animals, such as dogs<sup>10,12</sup>. The armadillo is known to be a reservoir of *P. brasiliensis*, and the fungus can be easily cultured from the animal's internal organs (spleen, liver, and lymph nodes), indicating a systemic process. *P. lutzii* has not yet been isolated from armadillos.

Epidemic outbreaks of PCM have never been observed. Further, fungal recovery (culture) directly from the fungi's environmental saprophytic form has been shown to be particularly difficult to obtain with reproducibility. Thus, the region where the disease is acquired is referred to as *reservaria*. Yet, sensitive molecular screening techniques have detected the fungus in soils and aerosols, especially among samples taken from animal burrows or sites with medium to high moisture content protected by vegetation cover<sup>13</sup>.

In recent decades, changes in the demographic characteristics and geographical distribution of PCM incidence have been observed. These shifts could be attributed to the rise of



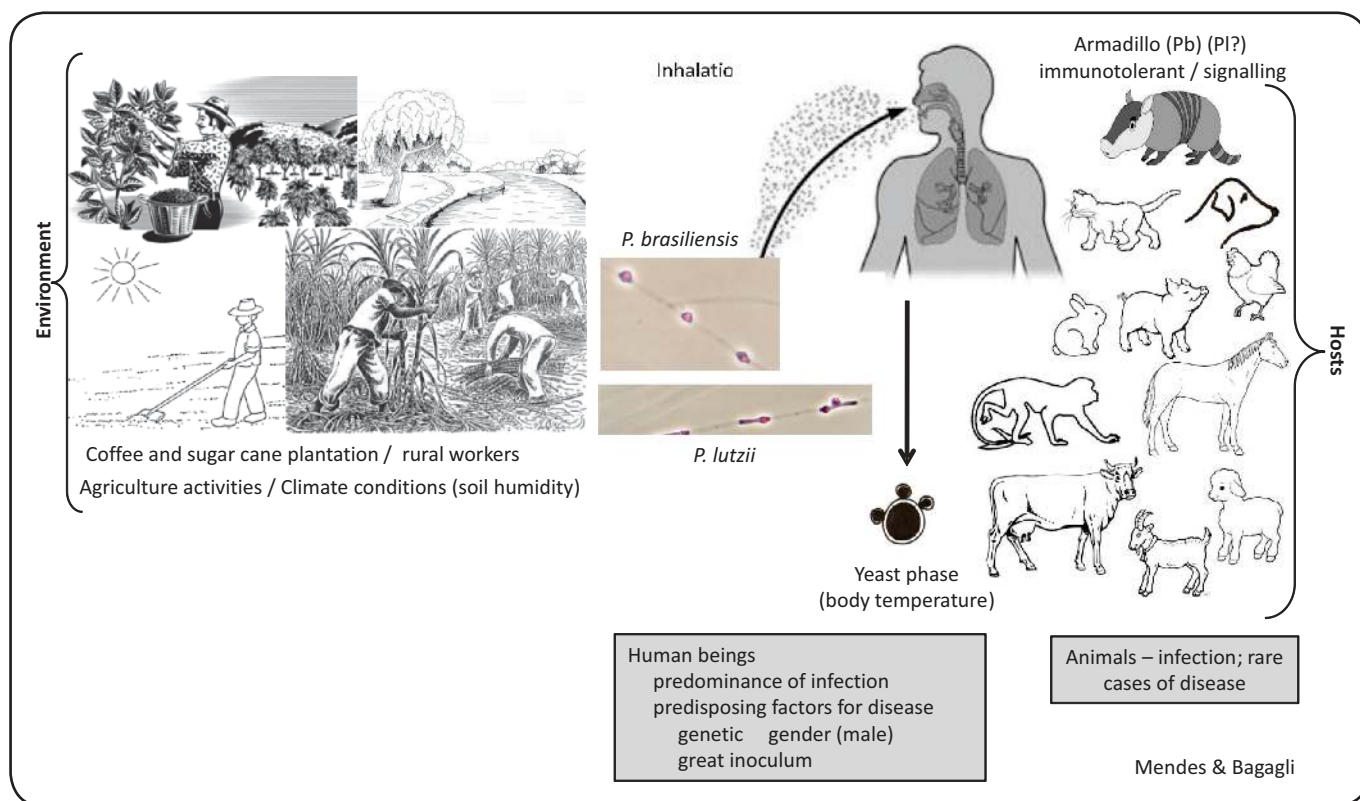
**FIGURE 1** - Geographic distribution of *Paracoccidioides lutzii* and *Paracoccidioides brasiliensis* cryptic species. Modified (update on *P. lutzii* distribution) from: Muñoz JF, Farrer RA, Desjardins CA, Gallo JE, Sykes S, Sakthikumar S, et al. Genome diversity, recombination, and virulence across the major lineages of *Paracoccidioides*. mSphere 2016; 1(5): e00213-163. PS2; PS3; PS4; S1a; S1b: phylogenetic species of *Paracoccidioides brasiliensis*; PI: *Paracoccidioides lutzii*.

urbanization, application of diagnostic methods, and the presence of comorbidities and immunosuppression. In addition, environmental factors, such as the expansion of settlements, clearing of forests, and increased coffee production, could contribute to the current high levels of PCM incidence in some regions of Rondônia<sup>14</sup>.

In addition, between 1982 and 1983, a region of Southeast Brazil experienced climatic changes related to El Niño, resulting in elevated soil moisture levels and temperatures between 18-28°C, which are favorable for fungal sporulation and aerial dispersion. During this same time period, the region experienced an outbreak of acute cases of PCM<sup>15</sup>.

### How is *Paracoccidioides* infection acquired?

The major risk factor for acquiring infection is a profession or activity related to the management of soil contaminated with the fungus, such as agriculture, earthworks, soil preparation, gardening, and transportation of vegetable products (**Figure 2**). In a majority of all PCM infection cases the patients had been exposed to agricultural activities during the first two decades of their life, at which point they likely acquired the infection even



**FIGURE 2** - Spread of *Paracoccidioides brasiliensis* and *Paracoccidioides lutzii*. Pb: *Paracoccidioides brasiliensis*; PI: *Paracoccidioides lutzii*.

if clinical manifestations appeared many years later<sup>11</sup>. Most of these patients sought medical attention many years after they left the endemic area and resided in urban centers where were engaged in other activities unrelated to soil management. For example, smoking (> 20 cigarettes/day for > 20 years) and alcoholism (> 50g/day)<sup>16</sup> are frequently associated with mycosis. Unlike other mycoses, such as cryptococcosis, disseminated histoplasmosis, and candidiasis, PCM is not usually related to immunosuppressive diseases. However, cases of PCM associated with HIV infection, neoplasia and, more rarely, organ transplants and use of immunobiologicals have been reported<sup>17-20</sup>.

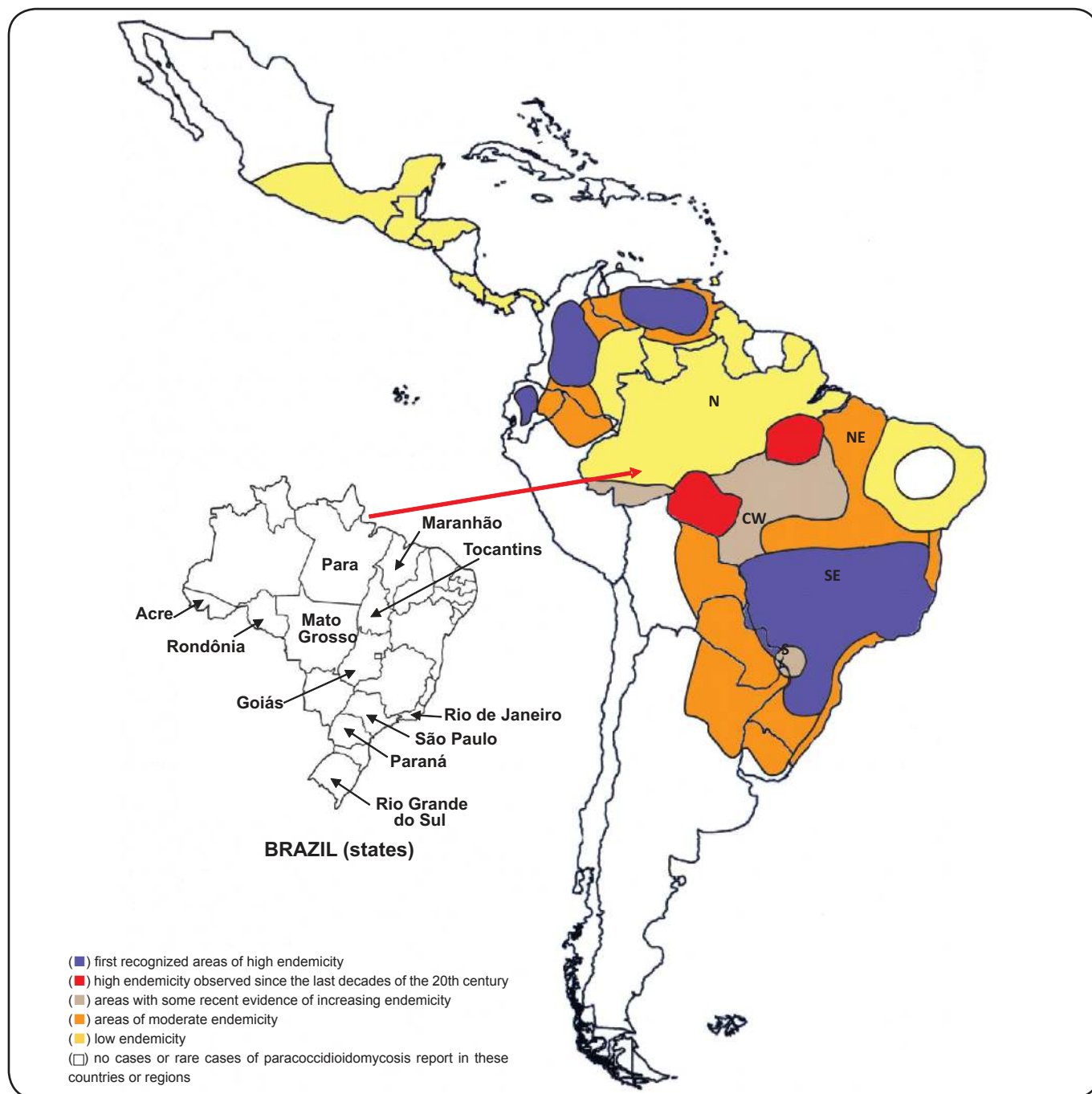
#### **Incidence, prevalence and mortality**

Since PCM is not a compulsory notification disease, we do not have precise data on its incidence in Brazil. Mycosis prevalence, incidence, and morbidity estimates are based on reports from epidemiological surveys, case series, hospitalization records, and mortality data<sup>21</sup>. Based on the experiences of reference services caring for patients with PCM, the disease's incidence in endemic areas ranges from three to four new cases per one million inhabitants and one to three new cases per 100,000 inhabitants per year. About 80% of PCM cases are registered in Brazil, particularly in the States of São Paulo, Paraná, Rio Grande do Sul, Goiás, and Rondônia (**Figure 3**)<sup>21</sup>. In Latin America, cases are most frequently reported in Argentina, Colombia, Venezuela, Ecuador, and Paraguay. Estimates of annual incidence in Brazil range from 0.71 to 3.7 cases per

100,000 inhabitants<sup>21</sup>. However, recent records of incidence in Rondônia report 9.4 cases per 100,000 inhabitants, with two municipalities reporting incidences close to 40 cases per 100,000 inhabitants<sup>14</sup>. Between 1980 and 1995, the Ministry of Health documented 3,181 cases of PCM-related deaths, resulting in a PCM mortality rate of 1.45 cases per one million inhabitants (2.59 for the South, 2.35 for the Midwest, 1.81 for the Southeast, 1.08 for the North, and 0.2 for the northeast regions)<sup>22</sup>. In this study, among all chronic infectious and parasitic disease, PCM was listed as the eighth highest cause of mortality and had the highest mortality rate among the systemic mycoses, even having a higher mortality rate than leishmaniasis. Recent data collected from 13,683 patients who were hospitalized with systemic mycoses between January 1998 and December 2006 showed that PCM accounts for the largest number of hospitalizations (49%) among all mycoses<sup>23</sup>, with emphasis on hospitalization rates in the north and Midwest regions, without major difference in the mortality of hospitalized patients (**Figure 3**).

#### **Age group and distribution between genders**

PCM infection is primarily acquired in the first two decades of life, with a peak incidence between 10 and 20 years of age. However, the presentation of clinical manifestations or evolution to disease is uncommon in this age group. Instead, PCM occurs more frequently in adults between the ages of 30- and 50-years-old as a result of endogenous latent foci reactivation<sup>10</sup>. Although the frequency of PCM cases ranges between regions, an estimated 10% of PCM cases occur in individuals under the



**FIGURE 3** - Geographical areas of paracoccidioidomycosis endemicity in Latin America. Reproduction from: Martinez R. New trends in Epidemiology. J Fungi. 2017;3(1):1<sup>21</sup>.

age of 20-years-old, while the remaining 90% occurring later in life. Further, in childhood, the frequency of PCM cases is evenly distributed between both genders, with a slight predominance in young male adults; however, in adulthood, the frequency ranges from ten to 15 men for one woman.

### IMMUNOPATHOGENESIS

Control of *Paracoccidioides* spp infection depends on the host's cellular immune response, with T cells playing a prominent role. PCM has a range of clinical presentations along a spectrum,

with each one being potentially associated with a specific T cell immunity pattern<sup>24</sup>. Most infected individuals living in endemic areas will not develop any illness. These individuals exhibit a T-helper [Th-1] immune response pattern characterized by the release of cytokines that activate macrophages, TCD4+, and TCD8+ cells, resulting in the formation of compact granulomas and control of fungal replication<sup>25,26</sup>; however, dormant forms of the fungus may still exist inside these granulomas. The few individuals who do develop the disease most likely had deficient Th-1 responses, with the extent of the failure correlating with



disease severity<sup>25,26</sup>. In fact, patients with infections that evolve to the more severe forms, such as the acute/subacute form disease (A) or eventually the severe disseminated chronic form (CF), develop Th-2 and Th-9 immune response patterns that do not form compact granulomas, but instead activate B lymphocytes, high levels of specific antibodies, including the IgE subclass, hypergammaglobulinemia, and eosinophilia<sup>27</sup>. Patients with the severe/disseminated unifocal or multifocal CF who bear lower fungal burdens, also exhibit deficient Th-1 responses, often at a lesser degree than that of patients with the AF or severe disseminated CF. In addition, these patients can still experience the formation of compact granulomas that can suppress, at least partially, fungal replication<sup>25,26</sup>. In these patients, the loss of Th-1 function would be partially compensated by the development of Th-17 and Th-22 responses, both of which drive intense mucosal inflammatory responses rich in neutrophils<sup>27</sup>. In fact, a characteristic feature of the CF is the involvement of the mucosa, especially in the respiratory tract. In addition, it has been demonstrated that regulatory T cells (Tregs) suppress T cell immunity and contribute to the T cell anergy observed in the more severe forms of the disease<sup>28,29</sup>.

The factors that determine the different outcomes of the PCM host-parasite interaction remain unknown. Preliminary data suggest that the host's immunogenetic background may play a role<sup>30</sup>. Regardless, clinical experiences have indicated that treatment of PCM should persist for long periods until effective cellular immune responses are elicited. However, for unknown reasons, yeast cells may remain in quiescent foci that can reactivate the disease and cause relapses. Usually, immune alterations subside with treatment and the protective Th-1 responses appear/reappear. This observation is corroborated by *in vitro* experiments that have demonstrated deficient Th-1 responses can be reverted<sup>31</sup>, although this response reconstitution has not been shown to reach the magnitude of that observed in healthy individuals without disease<sup>32</sup>. The role of the observed high serum levels of specific antibodies in any mechanism of protection could not yet be determined.

## CLASSIFICATION OF CLINICAL FORMS AND ASSESSMENT OF SEVERITY

PCM can compromise any organ, apparatus or system, as revealed in **Table 1**<sup>33,34</sup>, which presents clinical and autopsy findings. Further, PCM's diversification tends to hinder its classification.

Several classifications of PCM clinical forms have been published based on different criteria, such as lesion topography, disease natural history, severity of clinical presentation, and serological reaction results. This consensus adopted the classification presented in the *International Colloquium on Paracoccidioidomycosis* held in February 1986 in Medellin, Colombia<sup>35</sup>.

### I. Paracoccidioidomycosis infection

### II. Paracoccidioidomycosis (disease)

#### A. Acute/subacute form (juvenile)

- Moderate
- Severe

#### B. Chronic form (adult)

- Mild
- Moderate
- Severe

### III. Residual form or sequelae

## Paracoccidioidomycosis infection

Paracoccidioidomycosis infection is contracted when a healthy individual comes into contact with a *Paracoccidioides* spp. The infection is diagnosed by a positive intradermal reaction to specific antigens and necropsy findings of latent fungi<sup>36</sup>.

## Clinical forms of Paracoccidioidomycosis

### Acute/subacute form (juvenile)

The acute/subacute form of PCM is responsible for 5-25% of cases and may be more frequent in certain endemic regions while almost never observed in others. In Brazil, this form is more commonly observed in the following States: Maranhão, Minas Gerais, Pará, Goiás, and São Paulo.

The incidence of PCM appears to be declining in some endemic areas<sup>37</sup>. Acute/subacute PCM predominantly affects children, adolescents, and young adults, but can occur in adults between the ages of 30- and 40-years-old. The incidence of PCM tends to be evenly distributed between genders, especially among the adolescent population<sup>33,37-39</sup>.

This clinical form of PCM rapidly evolves and disseminates the infection to multiple organs and systems. In general, patients are diagnosed within a few weeks of symptoms onset. Most symptoms involve the phagocytic-mononuclear system, including the presence of localized or generalized lymphadenomegaly, which may present suppuration, fistulization, and hepatosplenomegaly. Symptoms may also include digestive manifestations, cutaneous (or mucosal) lesions, osteoarticular involvement, and rarely, pulmonary involvement. Fever, weight loss, and anorexia often accompany the clinical presentation. Intra-abdominal lymphadenomegaly may coalesce, producing tumor masses that exert compression on various organs, such as the bile duct and intestinal loops<sup>38</sup> (**Figure 4** and **Figure 5**). A prominent finding of laboratory alterations in this form is peripheral eosinophilia, which occurs in 30% to 50% of cases<sup>38-40</sup>. Under certain conditions, eosinophilia may be significant (up to 70% of peripheral blood leukocytes).

### Chronic form (adult)

The majority (74% to 96%) of PCM cases are in chronic form, which typically manifests in adults between the ages of 30- and 60-years-old (male to female ratio: 22:1). Chronic PCM initiates slowly and the symptoms often persist beyond 4 to 6 months, possibly even a year. In some cases, PCM develops without any physical indication, and the infection is only caught when the individual goes for a routine check-up or labor-related physical examinations. In 90% of patients with PCM, pulmonary impairment is observed<sup>41,42</sup>. After the lungs, the organs most affected by PCM are the mucosa of the upper aerodigestive pathway and skin (**Figure 6** and **Figure 7**).

**TABLE 1**  
Organs affected in paracoccidioidomycosis.

Organs	Clinical manifestation				Necropsies	
	Belissimo-Rodrigues et al [33]*		Franco et al [34]**		Franco et al [34]**	
	n	%	n	%	n	%
Lungs	778	63.8	128	74.0	24	96.0
Bronchus/trachea	5	0.4	.	.	.	.
Lymphadenomegaly	618		63	36.4	18	72.0
generalized	342	28.1				
localized	276	22.6				
Mouth, pharynx, larynx			83	48.0	15	60.0
oral mucosa	610	50.0				
larynx	196	16.1				
nasal mucosa	19	1.6				
Adrenals	26	2.1	6	3.5	11	44.0
Central Nervous System (CNS)	42	3.4	1	0.6	9	36.0
Liver			0	0.0	8	32.0
Spleen	57	4.7	0	0.0	7	28.0
Skin	361	29.6	22	12.7	6	24.0
Kidney			0	0.0	4	16.0
Bone marrow			0	0.0	3	12.0
Heart			0	0.0	3	12.0
Digestive tract	92	7.5	6	6.5	2	8.0
Testicles	9	0.7	1	0.6	2	8.0
Prostate			1	0.6	2	8.0
Eyes			2	1.2	0	0.0
Breast			1	0.6	0	0.0
Osteoarticular	27	2.2				

\*1,219 patients of the *Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (USP)*. \*\* 173 patients and 25 necropsies at the *Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP)*.



**FIGURE 4** - Acute form of PCM in children. A. Abscesses in frontal and clavicular regions resulting from osteo-articular involvement. B. Female child presenting with abscessed lymphatic involvement. C. Inguinal lymphadenomegaly. D. Lymphatic-abdominal involvement with ascites and hepatosplenomegaly. PCM: paracoccidioidomycosis. Reproduction with modification: Shikanai-Yasuda MA, Telles Filho F de Q, Mendes RP, Colombo AL, Moretti ML, Grupo de Consultores do Consenso em Paracoccidioidomicose. Consenso Brasileiro em Paracoccidioidomicose. Rev Soc Bras Med Trop. 2006;39(3):297-310<sup>39</sup>.



**FIGURE 5** - Patients with the acute/subacute (juvenile) form of PCM. A. Ganglionic mass in supraclavicular, cervical, and submandibular region. B. Lymphadenomegaly of PCM, which must be differentiated from hematological diseases, such as lymphoma. C. Verrucous ulcerative lesions on the face and pavilion caused by hematogenous dissemination. D. Papulonodular ulcerative lesions caused by hematogenous dissemination. PCM: paracoccidioidomycosis. Reproduction with modification: Shikanai-Yasuda MA, Telles Filho F de Q, Mendes RP, Colombo AL, Moretti ML, Grupo de Consultores do Consenso em Paracoccidioidomycose. Consenso Brasileiro em Paracoccidioidomycose. Rev Soc Bras Med Trop. 2006;39(3):297-310<sup>39</sup>.

Chronic PCM can be classified as either mild, moderate, or severe<sup>35</sup>. Severe cases are defined by meeting three or more of the following criteria: a) weight loss greater than 10% of the normal body weight; b) intense pulmonary involvement; c) involvement of other organs, such as adrenal glands, central nervous system, and bones; d) the presence of lymph nodes affected in multiple chains in superficial or deep, pseudotumoral form (>2.0cm in diameter, without suppuration) or suppurative form; e) high antibody titers.

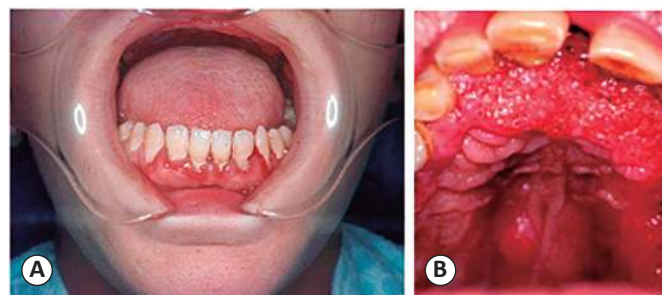
In fact, severe cases are represented by patients presenting clinical instability due to respiratory insufficiency, adrenal dysfunction, neurological syndrome or acute abdomen.

Mild cases, which constitute a small portion of patients, are those with weight loss below 5% of normal body weight and involvement of unique or a few organs or tissues without disfunction.

In some cases, patients present with clinical manifestations of both acute/subacute and chronic forms, making it difficult to properly classify the disease. Most of these patients present with intense suppression of cellular immunity and are labelled as having *mixed form* PCM<sup>43</sup>.

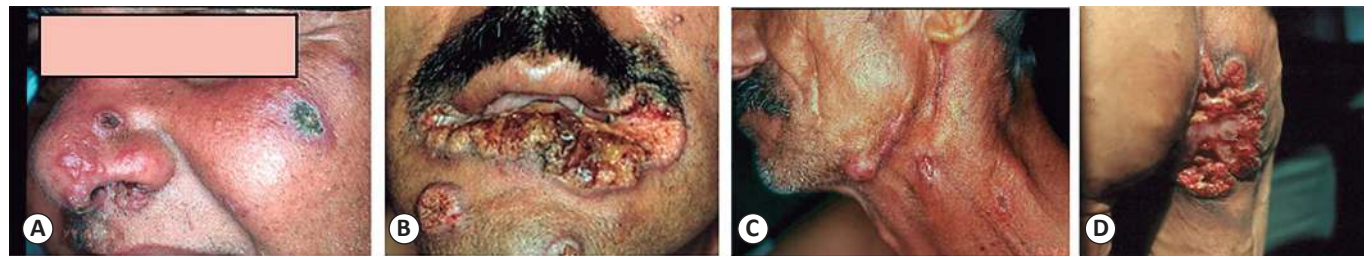
#### Residual forms (sequelae)

Residual forms, also referred to as sequelae, are clinical manifestations of anatomical and functional changes observed



**FIGURE 6** - Oral involvement in chronic PCM 47,48. A. Gingivostomatitis. B. Moriform stomatitis of Aguiar-Pupo. The lesions may present as extensive, ulcers, or ulcer-vegetative, with characteristic hemorrhagic dots (moriform lesion). Although infrequent, the lesions may extend into the nasal vestibule, causing perforation of the palate and nasal septum, with inesthetic and functional sequelae. In acute PCM, the oral mucosa is not frequently involved. PCM: paracoccidioidomycosis. Reproduction with modification: Shikanai-Yasuda MA, Telles Filho F de Q, Mendes RP, Colombo AL, Moretti ML, Grupo de Consultores do Consenso em Paracoccidioidomycose. Consenso Brasileiro em Paracoccidioidomycose. Rev Soc Bras Med Trop. 2006;39(3):297-310<sup>39</sup>.

after PCM treatment. Sequelae are observed in multiple organs, but have a higher rate of incidence in the lungs, skin, larynx, trachea, adrenals, mucosa of the upper aerodigestive tract, central nervous system, and lymphatic system, thus explaining the diversity of clinical presentation<sup>44-46</sup>.



**FIGURE 7** - Clinical aspects of chronic PCM. A. Papulonodular ulcerative lesions on the face. B. Perioral and mentonian involvement. C. Fistulated cervical and submandibular lymph nodes. D. Vegetative lesion with irregular borders in the perianal region. Through hematogenous dissemination, especially traumatic fungal implantation, the cutaneous lesions contiguously develop from compromised mucosa, fistulated lymph nodes, or bone involvement<sup>47</sup>. The lesions are characterized by ulcero-crusts polymorphisms, molluscoids, papules, or acneiforms, and are located primarily in the cephalic pole and periorificial regions<sup>48</sup>. Of note, patients with Addison's syndrome typically present with cutaneous and mucosal hyperpigmentation. PCM: paracoccidioidomycosis. Reproduction with modification: Shikanai-Yasuda MA, Telles Filho FQ, Mendes RP, Colombo AL, Moretti ML, Grupo de Consultores do Consenso em Paracoccidioidomycose. Consenso Brasileiro em Paracoccidioidomycose. Rev Soc Bras Med Trop. 2006;39(3):297-310<sup>39</sup>.



## INITIAL TREATMENT, DIAGNOSTIC APPROACH, AND OUTPATIENT FOLLOW-UP ROUTINE OF PATIENTS WITH PCM

Since PCM is systemic, any organ can be affected. The attention of the observer should initially be directed to the general condition of the patient and then the organs and systems that are most frequently committed according to the forms of the disease presentation: acute/subacute PCM and chronic PCM. According to routine medical care, all patients should have a detailed physical examination, reporting weight and height evaluation, to allow the characterization of nutritional status.

### General evaluation of a patient with acute/subacute form

In acute/subacute PCM, anamnesis and physical examination play an important role in the determination of disease severity and systemic involvement. For example, the presence of lymphadenomegaly in various lymphatic chains, hepatosplenomegaly, cutaneous lesions, or abdominal masses can be confirmed during a patient's physical examination. In addition, clinical examination can also detect the presence of jaundice, ascites, and peripheral edema, which prompt investigation of hypoalbuminemia. In acute/subacute PCM, signs of adrenal and neurological involvement are rare. Fever, weight loss, and digestive complaints, such as abdominal pain, chronic malabsorptive diarrhea, and vomiting, are also quite frequent<sup>40</sup>. The presence of tumefaction or pain in the bone region requires the identification of bone lesions.

### Laboratory tests and imaging:

*Chest X-ray (posterior, anterior, profile)*

*Complete blood count and erythrocyte sedimentation rate (ESR)*

*Liver biochemical tests (alanine aminotransferase (ALT), alkaline phosphatase)*

*Total proteins and fractions*

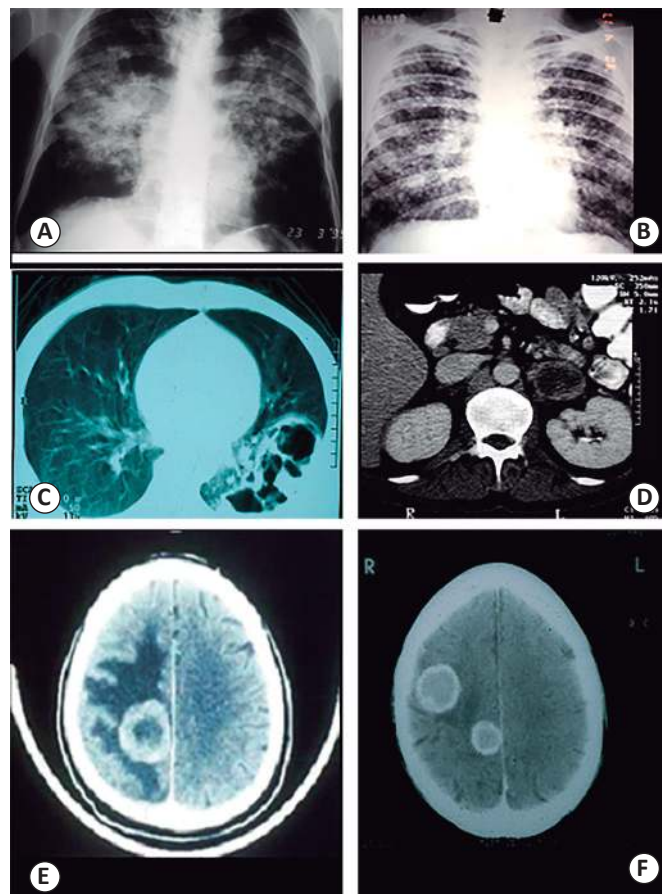
*Evaluation of renal and metabolic function (serum creatinine, Na, K)*

Imaging tests, such as ultrasound, CT, magnetic resonance imaging (MRI), and scintigraphic mapping should only be performed when there is clinical suspicion or laboratory results suggestive of organ involvement that cannot be solely assessed by physical examination.

### General evaluation of a patient with chronic form

In chronic PCM, anamnesis and physical examination must include the evaluation of signs and symptoms related to pulmonary, tegumentary, and laryngeal involvement<sup>41,46</sup> (cough, dyspnea, mucus/purulent expectoration, ulcerated lesions of the skin and naso-oropharyngeal mucosa<sup>47,48</sup>, odynophagia, dysphagia, and dysphonia). Both diagnostic methods must also evaluate signs and symptoms of lymphatic adenomegaly, adrenal involvement<sup>49,50</sup> (asthenia, weight

loss, hypotension, skin darkening, abdominal pain), central nervous system involvement<sup>51,52</sup> (headache, motor deficit, convulsive syndrome, and alteration of behavior and/or level of consciousness), and digestive impairment (diarrhea and malabsorption syndrome)<sup>53,54</sup> (Figure 8).



**FIGURE 8** - Images of PCM. A. Conventional *butterfly wing* radiological image showing bilateral, parahilar, and symmetrical pulmonary involvement with a predominance of alveolar lesions, sparing apices and lower thirds. These manifestations are very suggestive of PCM but occur infrequently. B. Diffuse and symmetric nodular and micronodular opacities. C. Computed tomography (CT) of lungs with multiple sub-pleural cavities. Pulmonary lesions may be interstitial of the thin or coarse reticular-nodular type, or, less frequently of the tumor type. D. Bilateral adrenal increase. E and F. CNS: hypodense and ring-shaped contrast enhancement images with small mass effect. PCM: paracoccidioidomycosis. Reproduction with modification: Shikanai-Yasuda MA, Telles Filho F de Q, Mendes RP, Colombo AL, Moretti ML, Grupo de Consultores do Consenso em Paracoccidioidomycose. Consenso Brasileiro em Paracoccidioidomycose. Rev Soc Bras Med Trop. 2006; 39(3): 297-310<sup>39</sup>.

### Laboratory tests and imaging

*Chest X-rays (posterior; anterior; profile)*

*Complete blood count and erythrocyte sedimentation rate (ESR)*

*Liver biochemical tests (ALT, alkaline phosphatase)*

*Evaluation of renal and metabolic function (serum creatinine, Na, K)*

More complex examinations should be conducted if there is a clinical suspicion or laboratory result suggesting central nervous system involvement, gastrointestinal involvement, abdominal forms, chronic respiratory insufficiencies, or osteo-articular lesions. In patients presenting with these signs,



imaging and functional tests should be performed under the guidance of medical experts. Given the high frequency of adrenal involvement and its clinical impact, patients suspected of having chronic PCM should undergo an assessment of the functional reserve when available.

### Differential diagnosis

Other conditions to consider in the differential diagnosis for PCM include the following: acute lymphoma, leukemia, histoplasmosis, tuberculosis, toxoplasmosis, visceral leishmaniasis, and infectious mononucleosis. For chronic cutaneous-mucosal PCM, the conditions to consider in the differential diagnosis are cutaneous or mucosal leishmaniasis, tuberculosis, chromoblastomycosis, leprosy, sarcoidosis, lues, neoplasia and in the chronic pulmonary form, tuberculosis (Table 2)<sup>55</sup>, coccidioidomycosis, histoplasmosis, sarcoidosis, pneumoconiosis, and interstitial pneumonitis. For digestive

PCM, conditions to consider in the differential diagnosis are tuberculosis and Chron's disease, while for forms of PCM that affect the central nervous system, the conditions are tuberculosis, cryptococcosis, cysticercosis, and neoplasias.

### Laboratory examinations for specific diagnosis

The identification of *Paracoccidioides* spp. through the examination of fresh sputum or other clinical specimens, such as lesion sample, lymph node aspiration, or biopsy fragment, is the gold standard for PCM diagnosis.

Aspects of PCM laboratory diagnosis are presented in Figure 9.

In an attempt to standardized PCM diagnosis, the following definitions are offered:

**Suspected case:** patient presents with one or more of the following manifestations, excluding tuberculosis and other

TABLE 2

Pulmonary involvement: differences between tuberculosis and paracoccidioidomycosis\*.

Epidemiology	Tuberculosis	Paracoccidioidomycosis
Age	Wide range	Restricted (30- to 60-years-old)
Gender	Indistinct	Prevalent in males (15:1)**
Incidence	45/100,000	1-3/100,000
Mortality	2.3/100,000	1.65/1,000,000
Geographic distribution	Worldwide, more urban	Latin America, more rural
<b>Microbiology</b>		
etiologic agent	<i>Mycobacterium tuberculosis</i>	<i>Paracoccidioides</i> spp.
source of infections	Man/animal	Soil
infection	Contagious	Non-contagious
cultivation	Fastidious	Fastidious
<b>Clinical aspects</b>		
signs and symptoms	Well defined	Non-specific
weight loss	++/++++	++/++++
fever	++++	+/-***
cough	++++	+/-
hemoptoic sputum	+++ /++++	+/-
pleural involvement	Yes	No
association	PCM (10-15%)	TB (10-15%)
<b>Radiology</b>		
image localization	Predominance in upper zone	Predominance in medium thirds, bilateral, and diffuse zones
cavities	+++ /++++	++ /++++
pleural images	Yes	No
dissemination	Uni/multifocal	Uni/multifocal
<b>Laboratorial changes</b>		
red cells	Normocytic normochromic anemia	Normocytic normochromic anemia
white cells	Leukocytosis/leukopenia	Leukocytosis/leukopenia
ESR	+++ /++++	+/+
serum proteins	Normal/low	Normal/low
<b>Natural evolution</b>	+++	+++
consumption	Yes	Yes
anergy	Yes	Yes
death	Yes	Yes

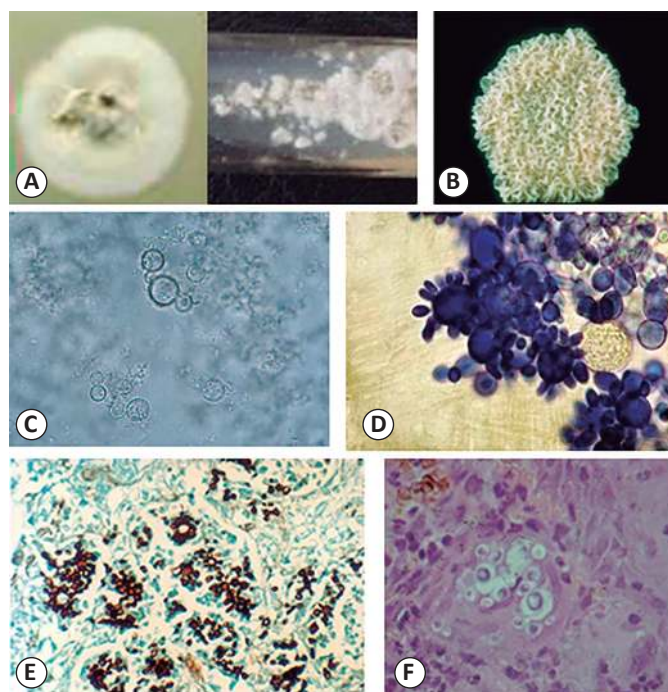
\* Modified from: Queiroz-Telles F and Escuissato D. Pulmonary paracoccidioidomycosis. Semin Respir Crit Care Med. 2011;32:764-74<sup>55</sup>. \*\*Pneumonia may occur rarely in acute/subacute PCM. In these cases, both sexes can be affected; \*\*\*Fever may occur in patients with associated infections. PCM: paracoccidioidomycosis; TB: tuberculosis; ESR: erythrocyte sedimentation rate.

diseases that occur with a similar condition, for at least four weeks:

- Cough with or without sputum and dyspnea
- Sialorrhea, odynophagia, or hoarseness
- Lesion (ulcerated) in the nasal or oral mucosa
- Skin lesions (ulcers, vegetation, nodules, plaques, etc.)
- Cervical or generalized adenomegaly, with or without suppuration and fistulization.
- Child or young adult with hepatosplenomegaly and/or abdominal tumefaction

**Probable case:** a patient with clinical manifestations compatible with PCM and anti-*P. brasiliensis*/*P. lutzii* serum antibody titers detected preferably by quantitative double immunodiffusion test or counterimmunoelectrophoresis.

**Confirmed case:** Patient with clinical manifestations compatible with PCM with secretions, bodily fluids, or lesion material presenting with fungal elements suggestive of *P. brasiliensis*/*P. lutzii* infection (**Figure 9**). Note, the micromorphology of *P. brasiliensis*/*P. lutzii* parasitic forms in the biological material of infected patients cannot distinguish between the two species. Therefore, the identification of the involved species requires culture isolation and application of molecular techniques<sup>56,57</sup>.



**FIGURE 9** - Laboratory diagnosis of paracoccidioidomycosis. A and B. Cultivation of *P. brasiliensis*. A. mycelial phase. B. yeast phase. C. Fresh examination in KOH. D. Lactophenol staining showing yeast cells with multiple buds. E. Histological section stained by the Grocott method. F. Histological section stained by PAS. KOH: Potassium hydroxide; PAS: Periodic acid - Schiff stain. Reproduction with modification: Shikanai-Yasuda, MA, Telles Filho F de Q, Mendes RP, Colombo AL, Moretti ML, Grupo de Consultores do Consenso em Paracoccidioidomicose. Consenso Brasileiro em Paracoccidioidomicose. Rev Soc Bras Med Trop. 2006;39(3):297-310<sup>39</sup>.

### Critical evaluation of serological tests: serologic diagnosis and follow-up

Specific serological tests are important in not only the diagnosis of PCM, but also in the assessment of host response to specific treatments. Currently, double immunodiffusion (DID), counterimmunoelectrophoresis (CIE), immunoenzymatic assays (ELISA), and immunoblots (IB) are the serological tests available in different reference services<sup>58-60</sup>.

These tests use standardized techniques and adequate antigens<sup>61</sup>, and display a sensitivity between 80% and 95%. The titer of specific anti-*P. brasiliensis* antibodies<sup>58,59,60</sup> correlates with the severity of the clinical forms, with higher levels detected in the acute/subacute and disseminated forms. In cases of PCM caused by *P. lutzii*, such information remains unknown, which has motivated multicenter studies in endemic areas. PCM cases with false negative results from any of the previously mentioned tests are most often associated with very localized lesions and hosts with AIDS or immunodepressive conditions. Antigens prepared from *P. brasiliensis* that are rich in gp43KDA<sup>62</sup> have excellent accuracy in the diagnosis of *P. brasiliensis* infections<sup>58-60</sup>, but have a low sensitivity in the diagnosis of *P. lutzii* infections<sup>63,64</sup>. These serological tests display a specificity between 85% and 100%, with immunodiffusion having the highest rate of specificity. False-positive reactions may occur in sera from patients with histoplasmosis, and eventually aspergillosis and leishmaniasis; however, gel immunodiffusion provides the highest rate of specificity for these conditions.

Currently, the main method of PCM serological diagnosis is double agar gel immunodiffusion (DID) because of its simplicity, cost-effectiveness, sensitivity (>80%), specificity (>90%), and extensive application over the last decades. For DID, or any other test used in the diagnosis of PCM, serums should be titrated to increase the accuracy of therapeutic response interpretation because antibody titers progressively decrease with successful clinical control. To meet serological cure criteria, negative or stabilization results at a dilution of 1:2 or less should be achieved. In certain cases, patients may already have titers below 1:4 upon diagnosis; therefore, the serological criteria will have limited value during treatment follow-up. Additional resources and techniques for PCM diagnosis have been developed, but they are not available for PCM routine assessment. These examinations include the immunoblot technique, the triage ELISA test, the detection of specific antigens and PCR<sup>65,66</sup>.

To date, there are no validated serological techniques for the accurate diagnosis of infection by *P. lutzii*. Unfortunately, there is no commercial system available for PCM diagnosis, and all available tests are based on systems developed *in house*<sup>58-60,63,64</sup>. A recent study revealed a large variability in the mycosis diagnostic results generated by serological tests performed at different reference laboratories<sup>67</sup>. Thus, to ensure precise assessment, follow-up serological response curves to antifungal treatments should be performed by the same technique and laboratory.

### Frequency of outpatient visits and completion of examinations

During the first 3 months of infection, monthly consultations are recommended to optimize patient adherence to the established regimen, to assess drug tolerability, and to ensure good clinical response (**Table 3**). If a satisfactory clinical response is observed, the consultations should become quarterly until the end of the first year. After 90 days of follow-up if a satisfactory clinical response is observed, patients should undergo complete blood count and biochemical tests every 3 months during the first year. Radiological and serological examinations should be requested every 6 months, or at shorter intervals if a satisfactory clinical response is not observed or if laboratory results indicate no change in activity. The reduction of specific antibody titers should occur approximately 6 months after treatment and should be either negative or stabilized at low titers for approximately 10 to 24 months after treatment. These estimations depend on the

clinical form, severity, and antifungal treatment administered, as itraconazole promotes a faster response than cotrimoxazole in the acute form rather than the chronic form. In the second year of follow-up, the consultations should become semi-annual. Once the cure criteria have been met, treatment should be discontinued and patients should be followed-up on an outpatient basis for up to two years. After this period, if the patient continues to meet cure criteria, the patient can be released from outpatient follow-up and instructed to return if necessary.

According to the clinical presentation of PCM, specific follow-up examinations, such as ultrasound (e.g. to evaluate the evolution of nodal masses or nodular images in abdominal organs), and CT, or MRI to evaluate cephalic lesions should be requested.

### Clinical specialty outpatient support

Patients with PCM that involves the larynx (dysphonia) and trachea should be referred to an otorhinolaryngologist

**TABLE 3**

Guidance for clinical-laboratory follow-up of patients with paracoccidioidomycosis undergoing therapy.

Examinations	1 <sup>st</sup> medical appointment	1 <sup>st</sup> , 2 <sup>nd</sup> , 3 <sup>rd</sup> month	6 <sup>th</sup> , 9 <sup>th</sup> , 12 <sup>th</sup> month	18 <sup>th</sup> , 24 <sup>th</sup> month	≥ 2 years 6/6 months	>1 year after treatment interruption: 6/6 months*
Medical appointment	X	X	X	X	X	X
Hemogram, ALT, Alkaline phosphatase Na, K creatinine	X	3 <sup>rd</sup> month	X	X	X	X
Erythrocyte sedimentation rate	X	X				
Serology	X		6 <sup>th</sup> , 12 <sup>th</sup>	18 <sup>th</sup> , 24 <sup>th</sup>	X	X
Thorax X-ray	X	X	6 <sup>th</sup> , 12 <sup>th</sup>	X*	X*	If necessary**

ALT: alanine aminotransferase; Na: sodium; K: potassium. \* After 1 year of treatment discontinuation, the patient should be released from follow-up if cure criteria has been met. \*\*Thorax X-ray: according to the presence of changes.



for evaluation and specialized examinations, such as nasofibroscope, for early diagnosis and treatment of complications.

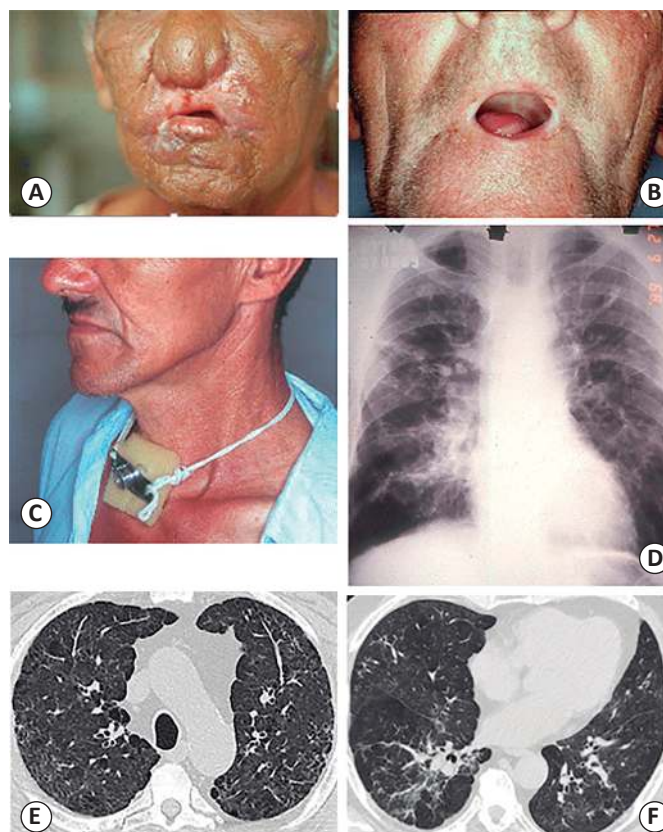
Despite adequate treatment and satisfactory therapeutic response, patients who develop persistent dyspnea associated with cutaneous and mucosal lesion scarring and body weight recovery should be referred to a pulmonologist to treat cicatricial lung disease or associated respiratory pathologies.

Similarly, patients with Addison's syndrome caused by adrenal impairment as a result of active or residual PCM should be followed up by an endocrinologist, especially those patients who were unresponsive to usual treatments. Patients with PCM with neurological, intestinal, or abdominal lymphatic involvement, accompanied by malabsorption syndromes, reproductive organ lesions, or other clinical situations, should be followed-up by a specialized physician because management of disease in these patients often presents additional difficulties.

## INDICATIONS FOR HOSPITALIZATION

The following types of patients must be hospitalized:

1. Patients with disseminated forms presenting one of the following complications: neurological alterations, respiratory insufficiency, nutritional status deficiency, gastrointestinal involvement, jaundice, ascites, or hemodynamic changes.
  - Patients presenting comorbidities, such as AIDS, tuberculosis, and/or neoplasia, and if there is a need for better diagnostic investigation or observed clinical deterioration.
  - Patients with sequelae and clinical instability, such as decompensated COPD, cor pulmonale, Addison's disease, laryngeal, or tracheal stenosis (Figure 10).



**FIGURE 10** - Sequelae of PCM in the respiratory system. A and B. Microstomia resulting from perioral lesions. C. Tracheostomy as a result of tracheal stenosis. D. Chest X-ray showing residual bilateral reticular infiltrate. E and F. CT showing post-treatment septal thickening, peripheral reticulation, and peribroncovascular thickening. PCM: paracoccidioidomycosis. Reproduction with modification: Shikanai-Yasuda, MA, Telles Filho F de Q, Mendes RP, Colombo AL, Moretti ML, Grupo de Consultores do Consenso em Paracoccidioidomycose. Consenso Brasileiro em Paracoccidioidomycose. Rev Soc Bras Med Trop. 2006;39(3):297-310<sup>39</sup>.

infection, sputum smear microscopy is recommended to evaluate the occurrence of tuberculosis, especially when there is pulmonary infiltrate affecting the upper lobes.

## ASSESSMENT OF COMORBIDITIES AND IMMUNOSUPPRESSION

Many patients with chronic PCM are smokers and present with chronic obstructive pulmonary disease (COPD) prior to the diagnosis of mycosis. Other diseases are relatively common in patients with PCM, particularly chronic infectious parasitic diseases and neoplasias. Predisposing factors of PCM are believed to promote the occurrence of certain diseases, including tuberculosis, leishmaniasis, Chagas disease, leprosy, and strongyloidiasis<sup>33</sup>. Further, *Paracoccidioides* spp. may be opportunistic in patients with reduced cellular immunity as a result of underlying disease or immunosuppressive treatments.

### Tuberculosis

Tuberculosis has been reported in approximately 2% to 20% of PCM cases, and the disease can be diagnosed before, after, or concurrently with PCM. When the two infections occur simultaneously, difficulties may arise in the diagnosis, selection of antifungal therapy, and recognition of therapeutic response<sup>68</sup>. In patients with lung injuries related to *Paracoccidioides* spp.

### Cancer

Several studies have reported that between 0.16% and 14.1% of patients with PCM also present with a neoplasm at some point in their lives<sup>19</sup>. Carcinomas were observed more frequently in the lungs, oropharynx, and larynx. Patients with *Paracoccidioides* spp.-related airway lesions may develop carcinomas at or near the fungal lesion several years later<sup>19</sup>. Whether PCM represents a risk factor for cancer or if both diseases have similar predisposing factors remains controversial. In patients with PCM, the frequency of cancer is higher in smokers than in nonsmokers<sup>69</sup>. Diagnostic suspicion is fundamental for early diagnosis and treatment because clinical manifestations of cancer in patients with PCM can be masked by symptoms resulting from sequelae of fungal lesions in the lungs, larynx, or pharynx, especially in smokers and alcoholics. Less frequently, PCM manifests simultaneously or reoccurs with neoplasias, such as lymphoma, leukemia, and pulmonary carcinoma<sup>19,70</sup>. This PCM is probably opportunistic and presents with localized lesions, particularly in the lung or disseminated.

These patients are generally treated with antifungal therapy and any deaths are attributed to neoplasia. In areas endemic to PCM, this mycosis should be considered in cases of cancer patients experiencing clinical worsening.

### **Organ transplantation and immunosuppressive therapy**

Opportunistic PCM has been observed in patients with reduced cellular immunity as a result of renal or hepatic transplantation, use of immunosuppressants, such as corticosteroids and cytotoxic and immunobiological drugs for the treatment of several diseases, or, in rare cases, primary immunodeficiency. This is exemplified by a case report of rheumatoid arthritis and bone sarcoma in which the patient was medicated with adalimumab, methotrexate, and leflunomide, and presented with lung and bone disease related to *Paracoccidioides* spp. infection<sup>20</sup>. In a small number of cases, PCM manifested a few days to 14 years after kidney transplantation, which enabled the evaluation of PCM's clinical and laboratory characteristics under these conditions. Chest X-rays revealed that these patients had bilateral nodules<sup>18</sup>, pulmonary cavitation<sup>71,72</sup>, or bronchopneumonic infiltrate<sup>73</sup>. Lymphatic impairment was uncommon<sup>74</sup>. In these cases, microbiological diagnosis should be preferential because serological tests generally show low titers of anti-*Paracoccidioides* spp. antibodies<sup>73,75</sup>. As in other immunosuppressed patients, unusual clinical and serological expressions may confuse and delay the diagnosis of PCM. In addition, the response to therapy in renal transplant patients may be slow, especially with the administration of oral antifungal agents<sup>72-74</sup>. In half of these cases, death was reported. The use of effective and intravenous antifungal agents is thus recommended, as well as rigorous monitoring of immunosuppressed patients who have been exposed to areas endemic to PCM.

### **HIV infection and AIDS**

Opportunistic PCM has been observed in HIV-infected patients, with up to 1.5% of Brazilian AIDS cases reporting simultaneously PCM infection<sup>17,76</sup>. In these co-infected patients, PCM progresses more rapidly and lesions are more widespread, involving lymphadenomegaly, umbilicated cutaneous lesions, hepatosplenomegaly, pulmonary infiltrates, and lesions of the central nervous system and other tissues. Most cases present mixed clinical manifestations with lesions predominantly of acute/subacute PCM, but with frequent pulmonary lesions, which may be atypical<sup>43</sup>. Many patients have a low CD4 + lymphocyte count and may present PCM as the first manifestation of AIDS. Although about 30% of the cases do not present anti-*Paracoccidioides* spp. antibodies, the fungus is easily recognized or isolated in mycological or histopathological examinations. HIV/*Paracoccidioides* spp. co-infection can lead to death, but most patients can be cured with intensive antifungal treatment combined with antiretrovirals and secondary prophylaxis<sup>17</sup>.

### **Recommendations for patients suspected of comorbidities and immunosuppression**

1. Request an acid-fast bacilli smear and culture in three samples of sputum from patients with pulmonary PCM, particularly those patients who present with fever, night

sweats, and infiltrate and/or cavitation in the upper lobes of the lungs.

2. Perform an otorhinolaryngological follow-up in patients with laryngeal lesions that persist with dysphonia to perform a differential diagnosis with tuberculosis or neoplasia.
3. In patients with pulmonary involvement and declining respiratory function despite appropriate treatment, the following conditions should be considered: bacterial infection, smoking-related lung disease (COPD), or associated neoplasia or sequelae with functional consequences.
4. Investigate a possible HIV infection in patients with suggestive epidemiology and in patients with acute/subacute or mixed form PCM.
5. In immunocompromised patients, the absence of antibodies, even in disseminated disease, does not rule out the diagnosis of PCM, which should be investigated with microbiological testing, and, if possible, with tissue biopsy and histopathological examination.

## **SEQUELAE**

PCM is a systemic disease whose host response to the infecting agent consists of chronic granulomatous inflammation associated with an overlying fibrosing process. Thus, in addition to granuloma formation, there is an increased production of cytokines, including TNF- $\alpha$  and TGF- $\beta$ , which can induce collagen and reticulin accumulation in the infected tissue. This fibrosing response may then lead to anatomical and functional changes in the organs affected during infection, especially the lungs.

### **Pulmonary**

Despite treatment, chronic PCM may continue to present symptoms, such as varying degrees of cough, hyaline expectoration, and dyspnea<sup>41,42</sup>. In addition, changes in spirometry, including an obstructive pattern, may also be observed in most cases, which is justified by the association of peribronchial fibrotic sequelae with the history of smoking in most patients<sup>42</sup>. A complete lung function test may also show air trapping and diffusion reduction, which in more severe cases can lead to chronic hypoxemia<sup>42</sup>. Most patients, even after completing treatment, show scarring alterations upon imaging tests, especially CT scans<sup>44</sup> (**Figure 10**), which can reveal architectural distortion (90%), septal and reticulated thickening (88%), centrolobular or paraseptal emphysema (82%), bronchial thickening (82%), parenchymal bands (74%), scarring in emphysema areas (66%), nodules <3 cm (62%), and pulmonary cysts (10%)<sup>42</sup>. In gasometry, an increased alveolar-arterial O<sub>2</sub> gradient, hypoxemia, and hypercapnia may be present, with the latter signaling greater severity. Pulmonary hypertension is rare, and secondary to parenchymal changes.

### **Adrenal glands**

On average, adrenal impairment is observed in 56% of autopsied cases, ranging from 48.2% to 80.0%<sup>34,36</sup>. However, 15% to 50% of patients undergoing adrenal evaluation present with a hampered reserve, despite the absence of

clinical manifestations, and 3.5% of these patients present with Addison's disease, which requires frequent hormonal replacement therapy throughout one's life<sup>49,50</sup>.

### Larynx

Laryngeal sequelae are characterized by dysphonia, as hoarseness and alterations in airflow and indicate poor closure of the fibrotic vocal cords. These complications are associated with an increased risk of pulmonary infections by aspiration and even difficulty of socializing because the voice is so altered<sup>77</sup>. Sequelae of the trachea can lead to obstruction of the airway and subsequent respiratory insufficiencies that can require tracheostomy or even surgical correction of tracheal stenosis.

### Central nervous system

Patients frequently develop motor deficits, convulsive syndromes (epilepsy), and/or hydrocephalus. Cerebellar impairment occurs in about 20% to 30% of PCM cases with neurological involvement, and these cases often rapidly evolve to intracranial hypertension, which requires ventricular shunting<sup>51,52</sup>. Neurological forms of PCM have substantial risks for sequelae.

### Skin

Cutaneous sequelae can lead to esthetic and oral mucosa alterations and even microstomia, which require special care for patient feeding and surgical correction after antifungal treatment.

### Lymphatic

The sequelae of the abdominal lymphatic system can lead to obstructive jaundice, as a result of lymph node involvement in the hepatic hilum<sup>78</sup> and malabsorption syndrome of proteins and fats<sup>54,79</sup>. The social and economical cost of these complications has not been adequately evaluated by the scientific community or health authorities.

### Evaluation and follow-up of pulmonary sequelae

Patients with PCM that involves the lungs may present with persistent respiratory symptoms despite undergoing adequate treatment. Thus, the presence of respiratory sequelae in the lung that are associated with the pathologies or recurrence of PCM should be actively investigated in symptomatic patients<sup>80</sup>. Spirometry should be performed and, in the presence of an obstructive disorder, the introduction of bronchodilator medication is suggested, following guidelines for the treatment of COPD<sup>81</sup>. Chest X-rays and CTs not only aid in the investigation of associated pathologies, such as lung neoplasia, but also aid in the diagnosis of disease recurrence (onset or recrudescence of lesions with radiological signs of activity, such as nodules and masses with cavities and ground glass density nodules). Co-infections, especially tuberculosis (**Table 2** and **Table 4**), should be investigated through microbiological examinations of sputum and, if necessary, bronchoalveolar lavage. Arterial blood gas

**TABLE 4**  
Diagnostic approach to respiratory complaints in treated patients.

Main differential diagnoses	Sputum microbiology	Sputum cytology	Chest X-ray and tomography	Serum (antibody/antigen)
PCM – relapse	+ or – <i>Paracoccidioides</i>	-	Recurrence of previous lesions, radiological findings of activity*  + For PCM*	+ para PCM
Infectious diseases				
Fungi	+ or -	-	Variable: Chronic histoplasmosis, pulmonary cryptococcosis, and chronic cavitary aspergillosis	+ histoplasmosis/Aspergillosis antibodies, Antigenemia +: cryptococcosis
Bacteria	Gram +/- + or - Culture	-	Alveolar consolidation, air bronchogram, sometimes interstitial infiltrate	-
Tuberculosis	AFB + + culture	-	Centerlobular nodules, distr. segmentar or confluent micronodules, budding tree pattern, cavities: thick walls, upper thirds; pleural effusion	-
Neoplasia	-	+ neoplastic cells	Variable, neoplastic cells, with higher frequency of nodule or solitary mass excavated or not; localized atelectasis	-
PCM - sequela	-	-	Scarring emphysema, bronchial thickening, signs of interstitial fibrosis, and peribroncovascular.	Low titers possible in PCM sequelae

PCM: paracoccidioidomycosis; AFB: acid-fast bacilli; +: positive ; -: negative ; ±: positive or negative. \*Consolidation, frosted glass lesions, thick-walled cavities, thickening of alveolar septa, nodules, and confluent masses.



analysis may indicate the need for supplemental oxygen in cases of severe hypoxemia ( $\text{PaO}_2 < 55\text{mmHg}$ ), and should be requested in patients with hypoxemia measured via pulse oximetry<sup>81</sup>. In more advanced cases from a clinical, spirometric, or laboratory point of view, a pulmonologist should perform an evaluation to characterize the severity and orientation of the therapy.

## TREATMENT

Unlike other pathogenic fungi, *P. brasiliensis* and *P. lutzii* are susceptible to most systemic antifungal agents – even sulfonamide derivatives can inhibit their growth. There is no solid evidence to support primary or secondary resistance to the drugs used in PCM treatment. Therefore, several antifungal drugs have been shown to be effective in treating different clinical forms of the disease, including azole derivatives (ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole<sup>82-87</sup>), sulfonamide derivatives (cotrimoxazole, sulfadiazine, etc.)<sup>88</sup>, amphotericin B (formulations in deoxycholate, lipid and liposomal complex) for severe forms<sup>89-91</sup>, and even terbinafine<sup>92</sup>.

Despite the vast therapeutic arsenal available for disease management, itraconazole, cotrimoxazole (sulfamethoxazole/trimethoprim combination), and amphotericin B are more commonly used in clinical practice. There is currently no *in vitro* or *in vivo* evidence showing that PCM by *P. brasiliensis* and *P. lutzii* respond differently to the antifungal agents used in the treatment of the disease. Therefore, the therapeutic recommendations are valid for all patients with PCM.

Although Latin America has high PCM incidence, morbidity, and mortality rates, only two randomized clinical trials involving patients with PCM have been published. However, neither study had statistical power capable of identifying crucial definitions, such as efficacy, safety, and treatment duration<sup>83,86</sup>. Thus, the suggested guidelines for PCM treatment are based on only two prospective, open randomized studies, and multiple

retrospective or prospective, comparative or non-comparative studies<sup>82,86,90,93,94</sup>. Although tested in a small number of patients, voriconazole, posaconazole, and isavuconazole have been shown to have inhibitory action *in vitro* against *Paracoccidioides* spp. isolates, and therefore, these agents are potentially useful in the treatment of PCM. However, drug interactions and adverse events of prolonged therapy should be taken into account.

### Treatment of patients with mild and moderate forms

Itraconazole at a dose of 200mg daily has been widely used in the treatment of mild and moderate forms of PCM with high rates of efficacy and safety. Therefore, at present, this triazole is the treatment of choice for patients with mild to moderate forms of PCM. The duration of treatment may vary from 9 to 18 months, with an average duration of 12 months, and the patient should always be evaluated by clinical, immunological, and radiological criteria. (Table 5). In general, the tegumentary lesions heal 30 days after the start of treatment and the lymphadenopathies regress between 45 and 90 days. Stabilization of radiological images is usually observed after 6 months of itraconazole use.

As with many triazole fungicides, the absorption of itraconazole may be impaired by a number of factors, such as drug interactions, achlorhydria, previous gastrectomy, alkaline food intake, or fasted state (Table 5, Table 6, Table 7, and Table 8). For increased serum levels in adult patients, itraconazole capsules should be ingested in a single intake after lunch or dinner. Acidic beverages, such as citrus juices, can increase the absorption of itraconazole, while alkaline foods decrease absorption. Fractionated dosing of itraconazole is not recommended because its absorption from the gastrointestinal tract occurs only when the drug is packed in intact capsules. In terms of clinical efficacy (predominantly with chronic PCM), treatment duration and adherence, and pharmacoeconomics, several retrospective, comparative studies have shown that the treatment of PCM with itraconazole is more advantageous than treatment with sulfamethoxazole/trimethoprim (cotrimoxazole)<sup>93,94</sup>.

TABLE 5

Most commonly used drugs in patients with paracoccidioidomycosis.

Drugs	Dose	Average duration
Itraconazole*	200mg daily **Children < 30kg e > 5 years, 5 to 10mg/kg/day, adjust dose without opening the capsule	9-18 months
Cotrimoxazole*	Trimethoprim, 160mg + Sulfamethoxazole, 800mg (VO 8/8h or 12/12h) Children – Trimethoprim, 8 to 10mg/kg + Sulfamethoxazole, 40 to 50mg/kg, VO 12/12h	18-24 months***
Amphotericin B	Deoxycholate 0.5-0.7mg/kg/day (IV) Lipid formulation 3-5mg/kg/day (IV)	2-4 weeks**** (until improvement)

CNS: central nervous system. \*Do not use concomitantly with astemizole, antacids and H2 blockers, barbiturates, cisapride, cyclosporine, didanosine, digoxin, fentanyl, phenytoin, rifampicin, cisapride, and terfenadine. \*\*Increased experience in children with sulfamethoxazole/trimethoprim treatment. \*\*\*Extend the duration of treatment when there is CNS involvement. \*\*\*\*Requires maintenance treatment with itraconazole or cotrimoxazole.

**TABLE 6**  
Drug interactions of sulfamethoxazole + trimethoprim and amphotericin B.

Drugs	Sulfamethoxazole + Trimethoprim (SXT)	Amphotericin B
Azathioprine	Risk of leukopenia by medullary suppression Monitor	No interactions found
Aminoglycosides	No interactions found	↑ nephrotoxicity
(amikacin, gentamicin, tobramycin, netilmicin, and streptomycin)		Combination contraindicated
Cyclosporine	↓ cyclosporine ↑ risk of nephrotoxicity Avoid combination	↑ nephrotoxicity ↑ ototoxicity Combination contraindicated
Digoxin	↑ digoxin Use with caution	↑ risk of toxicity of digoxin if ↓K Monitor carefully
Phenytoin	↑ Phenytoin Use with caution and monitor	No interactions found
Isoniazid	No interactions found	No interactions found
Loperamide	No interactions found	No interactions found
Methotrexate	↑ toxicity methotrexate Avoid combination	No interactions found
Metformin	↑ Metformin Minor interaction	No interactions found
Rifampicin	↓ SXT – Monitor	No interactions found
Pyrimethamine	↑ risk of megaloblastic anemia Monitor	
Warfarin	↑ Warfarin effect Avoid combination	No interactions found
Thiazides	↑ risk of thrombocytopenic purpura Monitor	No interactions found

K: potassium; SXT: sulfamethoxazole-trimethoprim; **References:** <http://reference.medscape.com/drug-interactioncheck><sup>95</sup>; <https://online.epocrates.com/interaction-check><sup>96</sup>.

### New azole derivatives

Although only a small number of patients have been treated with other drugs on the expanded triazole spectrum triazoles, including voriconazole, posaconazole (with expected future use with extended release capsules), and isavuconazole, these drugs can be considered as potential substitutes for itraconazole as their costs become more affordable and new evidence is published<sup>86,87</sup>; however, drug interactions should be taken into account<sup>95,96</sup> (Table 6, Table 7 and Table 8).

#### Cotrimoxazole (sulfamethoxazole/trimethoprim)

Although cotrimoxazole is fungistatic and requires a longer treatment duration than that of itraconazole, cotrimoxazole is the second treatment option for patients with mild to moderate forms

of PCM. Cotrimoxazole's advantages include large availability within Brazil's public health system, tablet form, oral and venous formulations, and good absorption with predictable serum levels. The oral suspension can be used in children who do not tolerate tablets and in adults who do not swallow tablets because of stenotic laryngeal or esophagus lesions. The cotrimoxazole venous solution can be used in patients with digestive disorders and/or who do not absorb oral medication well. Cotrimoxazole can also be used in contraindications of itraconazole, or in cases of suspected therapeutic failure or concomitant tuberculosis treatment. According to a few published cases, cotrimoxazole is the treatment of choice for patients with neuroparacoccidioidomycosis<sup>52,97</sup>.

TABLE 7

Main drug interactions for azole antifungals.

Drugs	Fluconazole	Itraconazole	Ketoconazole	Voriconazole	Posaconazole
Amitriptyline	↑ QT *Avoid combination	↑ QT* Avoid combination	↑ QT*Avoid combination	↑ QT*Avoid combination	↑ QT*Avoid combination
Warfarin	↑ Warfarin Avoid combination	↑ Warfarin Avoid combination	↑ Warfarin Avoid combination	↑ Warfarin Avoid combination	↑ Warfarin Avoid combination
Calcium channel blockers	↑ blocker effect Combination not contraindicated	↑ blocker effect Combination not contraindicated	↑ blocker effect Combination not contraindicated	↑ blocker effect Combination not contraindicated	↑ blocker effect Combination not contraindicated
H2 blockers, antacids, sucralfate	No interactions found	↓ Itraconazole Avoid combination	↓ Ketoconazole Avoid combination	No interactions found	↓ Posaconazole Avoid combination
Carbamazepine	↑ Carbamazepine Monitor serum carbamazepine level  Use with caution	↑ Carbamazepine ↓ Itraconazole Monitor serum carbamazepine level  Use with caution	↑ Carbamazepine ↓ Ketoconazole Monitor serum carbamazepine level  Use with caution	↑ Carbamazepine ↓ Voriconazole Combination contraindicated	↑ Carbamazepine ↓ Posaconazole Monitor serum carbamazepine level  Use with caution
Cyclosporine	↑ Cyclosporine  Use with caution	↑ Posaconazole ↑ Cyclosporine Monitor clinical treatment	↑ Cyclosporine Monitor serum level	↑ Cyclosporine Monitor serum level	↑ Posaconazole ↑ Cyclosporine Monitor clinical treatment
Phenytoin	↑ Phenytoin Use with caution	↓ Itraconazole Avoid combination	↑ Phenytoin ↓ Ketoconazole Avoid combination	↑ Phenytoin ↓ Voriconazole Avoid combination or monitor	↑ Phenytoin ↓ Posaconazole Avoid combination
Isoniazid	No interactions found	↓ Itraconazole Monitor serum level	↓ Ketoconazole Combination contraindicated	↑ Voriconazole Monitor serum level	No interactions found
Proton pump inhibitors (omeprazole)	↑ effect of proton pump inhibitors Use with caution	↓ Itraconazole Avoid combination	↓ Ketoconazole Combination contraindicated	↑ effect of proton pump inhibitors Use with caution	↓ Posaconazole Avoid combination
Lovastatin / Simvastatin	↑ Lovastatin /  Simvastatin Combination contraindicated	↑ Lovastatin /  Simvastatin Combination contraindicated Risk of myopathy and rhabdomyolysis	↑ Lovastatin /  Simvastatin Combination contraindicated Risk of myopathy and rhabdomyolysis	↑ Lovastatin /  Simvastatin Combination contraindicated Risk of myopathy and rhabdomyolysis	↑ Lovastatin /  Simvastatin Combination contraindicated Risk of myopathy and rhabdomyolysis
Midazolam/ triazolam  oral	↑ Midazolam Risk of respiratory depression Avoid combination	↑ Midazolam Risk of respiratory depression Combination contraindicated	↑ Midazolam Risk of respiratory depression Combination contraindicated	↑ Midazolam Risk of respiratory depression  Avoid combination	↑ Midazolam Risk of respiratory depression  Avoid combination
Rifampicin/ rifabutin	↓ Fluconazole ↓ Rifampicin Consider increasing the dose of fluconazole	↓ Itraconazole ↓ Rifampicin Monitor treatment efficacy	↓ Ketoconazole ↓ Rifampicin  Monitor treatment efficacy	↓ Voriconazole ↓ Rifampicin Combination contraindicated	↓ Posaconazole ↓ Rifampicin Monitor treatment efficacy
Sirolimus	↑ Sirolimus Combination contraindicated	↑ Sirolimus Use with caution	↑ Sirolimus Combination contraindicated	↑ Sirolimus Combination contraindicated	↑ Sirolimus Combination contraindicated
Tacrolimus	↑ QT ↑ Tacrolimus Avoid combination	↑ Tacrolimus Avoid combination	↑ Tacrolimus Avoid combination	↑ Tacrolimus Use with caution	↑ Tacrolimus Use with caution

**References:** <http://reference.medscape.com/drug-interactioncheck><sup>95</sup>; <https://online.epocrates.com/interaction-check><sup>95</sup>; \*QT interval in electrocardiogram.



**TABLE 8**  
Drug interaction between antiretrovirals and azole antifungals.

Antiretroviral	Fluconazole	Itraconazole	Voriconazole	Posaconazole
<b>Zidovudine</b>	↓Zidovudine Minor interaction	No interactions found	No interactions found	No interactions found
<b>Tenofovir</b>	No interactions found	No interactions found	No interactions found	No interactions found
<b>Lamivudine</b>	No interactions found	No interactions found	No interactions found	No interactions found
<b>Efavirenz</b>	Minor interaction	↑Efavirenz	↑Efavirenz	↑Efavirenz
<b>(avoid combination with azoles)</b>		↓Itraconazole	↓Voriconazole	↓Posaconazole
<b>Dolutegravir</b>	No interactions found	No interactions found	No interactions found	No interactions found
<b>Darunavir</b>	↑Darunavir	↑Darunavir	↑Darunavir	↑Darunavir
	Avoid combination			
<b>Ritonavir</b>	↑Ritonavir Use with caution	↑Ritonavir; ↑Itraconazole	↑Ritonavir; ↓Voriconazole	↑Ritonavir; ↑Posaconazole
		Avoid combination	Combination contraindicated	
<b>Lopinavir/ritonavir</b>	↑Lopinavir ↑Ritonavir Avoid combination	↑Lopinavir ↑Ritonavir ↑Itraconazole	↑Ritonavir ↓Voriconazole Combination contraindicated	↑Lopinavir ↑Ritonavir ↓Posaconazole
		Avoid combination		Use with caution
<b>Atazanavir</b>	↑Atazanavir Minor interaction	↑Atazanavir ↑Itraconazole	↑Atazanavir Combination contraindicated	↑Atazanavir Minor interaction
		Use with caution		
<b>Abacavir</b>	No interactions found	No interactions found	No interactions found	No interactions found

**References:** <http://reference.medscape.com/drug-interactioncheck<sup>95</sup>>; <https://online.epocrates.com/interaction-check<sup>96</sup>>.

### Treatment of patients with severe and disseminated forms

For severe and disseminated forms of PCM, amphotericin B in deoxycholate or in lipid formulation (liposomal or lipid complex) is indicated for use. The recommended induction dose of conventional amphotericin B is 0.5-0.7mg/kg/day, with a maximum of 50mg/day. Lipid formulations should be prescribed at doses of 3 to 5mg/kg/day. The duration of treatment depends on the clinical stability of the patient and amphotericin B should be administered for the shortest possible time (on average 2 to 4 weeks). Transition to oral medication during the consolidation phase should occur after clinical stabilization once the drug's oral absorption has been confirmed.

If the lipid formulations of amphotericin B cannot be used, intravenous cotrimoxazole formulation is recommended at a dose of 800mg/160mg every 8 hours. Despite having little clinical experience, intravenous fluconazole (600 to 800mg/day) can also be a therapeutic option.

The main therapeutic challenges of PCM management are the continuous use of systemic antifungal agents for extended periods, the possibility of relapse, and the appearance of sequelae, mainly in the respiratory tract. In addition to the use of antifungal drugs, PCM therapeutic management should include measures that improve the patient's general condition, treatment of infectious or non-infectious comorbidities, application of cure criteria, and post-therapeutic follow-up.

### Corticosteroids

Although scarce, there is evidence in the literature that some patients with PCM may benefit from the use of corticosteroids concomitantly with antifungal treatment<sup>98</sup>. Patients that have been shown to benefit from this approach often have intense inflammation, either in the ganglia or central nervous system, serious lesions of the larynx or trachea, and lung lesions resulting in respiratory insufficiency. The use of prednisone for 1 to 2 weeks can reduce inflammation during therapy with antifungal

agents. In patients with PCM and AIDS who are administered antifungal and antiretroviral drugs but still present with worsening clinical symptoms, the possibility of immune reconstitution inflammatory syndrome (IRIS) may be taken into account, based on other infections associated with HIV/AIDS.

### General measures

All patients should be treated long enough to reduce signs and symptoms, stabilize body weight, have clear chest X-rays, and appropriate serum antibody titers. In addition to specific antifungal therapy, patients with severe forms of PCM need general measures to improve their nutritional status and immunosuppression. Regulating smoking, alcohol consumption, adrenal insufficiency, and other associated conditions also contribute to a better patient outcome. Therefore, the following factors are important in achieving PCM cured criteria: rest, a hyperproteic and hypercaloric diet supplemented with vitamins, alcohol and tobacco restriction, and treatment of Addison's disease and associated infections, such as enteroparasitoses and respiratory bacterial co-infections. However, these recommended measures are useless if the patient cannot access antifungal medication, which the majority of the individuals with PCM cannot do because of their socioeconomic status and inability to afford treatment. Therefore, in the future, outpatient medications (itraconazole and cotrimoxazole) should be provided free of charge.

### Therapy in special populations

#### Pregnancy

PCM can occur in pregnant women either as an initial manifestation or as a reactivation of a previously controlled fungal disease. PCM is believed to occur in pregnant women because of the reduction of immune responses in pregnancy, which also predisposes these women to other systemic mycoses. In one study, *Paracoccidioides* spp. disseminated to the placenta, but there were no reports of fetal involvement<sup>99</sup>. PCM in pregnant women is controllable with the usual antifungal agents, primarily amphotericin B (category B). However, with the possibility of a teratogenic effect, the use of azole drugs (category C) and sulfamethoxazole/trimethoprim (category D) should be avoided<sup>100</sup>. Amphotericin B (category B) and sulfadiazine (category C) are alternatives for use during all gestational periods, but sulfadiazine should be discontinued 15 days before the expected delivery date to avoid neonatal complications. Sulfamethoxazole/trimethoprim may be used during breastfeeding<sup>100</sup>. Antifungal therapy should be maintained throughout all gestational periods to prevent relapse and postpartum discontinuation should be assessed by the usual cure criteria. After birth, conventional antifungal therapy should be administered until the patient reaches the cure criteria.

#### AIDS

Patients with AIDS generally have severe and widespread forms of PCM; therefore, these patients should be initially treated with amphotericin B or, if appropriate, with high doses of itraconazole, 600mg/day (with attention towards interactions

with antiretroviral drugs) or intravenous sulfamethoxazole/trimethoprim (2 ampoules every 8 hours). Despite having limited clinical experience, intravenous fluconazole (600-800mg/day) may be a therapeutic option. To avoid possible drug interactions, PCM should be treated initially with antifungals for 3 to 5 weeks prior to initiation of antiretroviral therapy. Following the cure of PCM, secondary prophylaxis with sulfamethoxazole (1,600mg/day), trimethoprim (320mg/day), or itraconazole (200mg/day) is recommended based on the treatment of other mycoses in immunocompromised patients. Prophylaxis should continue until the administered antiretroviral therapy elevates the CD4 lymphocyte count to a minimum of 100 cells/ $\mu$ L (concomitantly with undetectable viral load) to 200 cells/ $\mu$ L, regardless of viral load for at least 3 months. The use of sulfamethoxazole/trimethoprim (800/160mg every 12 hours) is also effective as a primary and secondary prophylaxis for pneumocystosis and as primary prophylaxis for neurotoxoplasmosis. In immunosuppressed patients, the absence of antibodies, even in disseminated disease, does not rule out the diagnosis of PCM, which should be investigated with microbiological tests and, if possible, with tissue biopsy and histopathological examination.

### Hepatic or renal insufficiency

The doses of the drugs used in PCM treatment should be adjusted in patients with hepatic or renal impairment.

#### Renal insufficiency<sup>101-103</sup>

##### Amphotericin B

This drug should be avoided because of its high potential for nephrotoxicity, which is compounded with the use of consecutive series. Serum amphotericin B levels are not significantly affected by hemodialysis and do not require adjustment in these cases. One should opt for other drugs or a lipid formulation of amphotericin B.

##### Azoles

Since several azoles present renal excretion, their dose should be adjusted as follows<sup>101-103</sup>.

Fluconazole: this azole has 80% renal clearance, and when renal clearance is less than 50ml/min, the dose should be reduced to 50% and administered at intervals of 48 hours. If renal clearance is less than 20 ml/min, the dose should be reduced to one-third of the normal dose and administered at intervals of 72 hours. In the case of hemodialysis, the full dose should be used after the dialysis process and 50% of the normal dose should be used during peritoneal dialysis.

Itraconazole: when renal clearance is less than 10ml/min, the dose should be reduced to 50%. In the case of hemodialysis or peritoneal dialysis, 100mg of an oral solution should be administered every 12 to 24 hours.

Voriconazole: when creatinine clearance is more than 50ml/min, use a 6mg/kg loading dose every 12 hours twice, followed by a 4mg/kg/day every 12 hours. Do not use an IV solution when clearance is less than 50ml/min. In cases of renal replacement therapy, hemodialysis, or peritoneal dialysis use 4mg/kg/day every 12 hours.

Terbinafine: when clearance is greater than 50ml/min, administer a dose only every 24 hours, and avoid use when clearance is less than 50ml/min.

### **Sulphamidic derivatives**

Sulphamidic derivatives present renal excretion and their metabolites may cause toxicity because they are poorly soluble at an acidic pH (urine), resulting in the formation of crystals that are deposited in the renal tubules that can lead to obstruction and subsequent kidney damage. Cases of interstitial nephritis have also been reported. These derivatives can be removed by dialysis. As a result, these products should be avoided in patients with renal insufficiency.

### **Functional liver changes<sup>101-104</sup>**

PCM can cause functional liver changes via hepatocytic injury or extrinsic cholestatic compression<sup>104</sup>. In these cases, PCM treatment follows the proposed standards and the patient typically exhibits satisfactory responses. However, hepatotoxicity induced by antifungal agents may occur.

### **Amphotericin B**

This drug has been known to accumulate in organs, often remaining in the liver, but rarely leading to an increase in transaminases. Amphotericin B deoxycholate is slightly hepatotoxic, unlike its lipid derivatives, which have the disadvantage of displaying a higher hepatic toxicity. Liver failure does not cause significant retention of the drug, which maintains a stable serum level.

### **Azoles**

The biochemical changes observed with itraconazole persist with continued treatment. In treatment with cotrimoxazole and itraconazole, the commonly reported biochemical changes do not exceed 5x the upper limit of normality, which allows the maintenance of the treatment. However, there are case reports in which itraconazole had to be discontinued. Of the azoles, fluconazole is the least hepatotoxic.

### **Metabolized in the liver with contraindications relating to serious liver diseases**

Ketoconazole, voriconazole and Sulphonamides

Voriconazole and ketoconazole are the most hepatotoxic agents, followed by itraconazole<sup>105</sup>. Therefore, these agents should be avoided in cases of severe hepatic impairment. Fluconazole can be used with great caution if the patient cannot be treated with amphotericin.

### **Metabolized in the liver with adjusted doses relating to liver diseases**

Voriconazole should be administered at 6mg/kg every 12 hours for two doses, followed by a dose of 2mg/kg/day every 12 hours.

### **Sulphamidic derivatives**

These agents rarely cause severe hepatotoxic injury, and may be used. Despite treatment maintenance, liver toxicity induced by cotrimoxazole evolves with the normalization of serum

liver enzymes. In patients with hepatic impairment caused by other conditions, such as cirrhosis or alcoholic liver disease, amphotericin B deoxycholate should be used because it is less toxic to the liver than other preparations. An alternative agent is fluconazole.

### **Paracoccidioidomycosis in children<sup>39,40,106,107</sup>**

In children infected with PCM, the most commonly used treatment is the combination of sulfamethoxazole/trimethoprim because it has known efficacy, good tolerability, syrup-like presentation for dose administration and adequacy, and is provided by the public health network<sup>39,40,106</sup>. The recommended dose ranges between 8 to 10mg/kg/day of trimethoprim in two daily doses, and no fasting is required. Intravenous formulation is an alternative when the oral route is contraindicated, as in cases of intestinal subocclusion. The intravenous formulation should be administered at the same dosage twice a day. Among the side effects reported, leukopenia is frequent; however, this condition can be controlled without other associated complications with the concomitant use of folic acid<sup>106</sup>.

Itraconazole may be used as a second option at a dose of 5 to 10mg/kg/day once daily. Amphotericin B deoxycholate, as well as other formulations of amphotericin B, is reserved for severe cases<sup>108</sup>. During treatment, some patients may present with a paradoxical reaction characterized by clinical worsening, such as new lymph node enlargements, fistulization, fever, and weight loss. In this case, steroids should be administered<sup>108</sup>.

### **Paracoccidioidomycosis in situations of limited resources**

In Rondônia, a systematic registry of PCM cases has been maintained since 1997, with periods of more than 15 cases per 100,000 inhabitants occurring over the years. In the stratified analysis by municipality, periods of almost 40 cases per 100,000 inhabitants were documented in the southern region of the state<sup>14</sup>.

Individuals with PCM who are rural workers with low levels of education, precarious socioeconomic statuses, and difficulty assessing health care services are susceptible to delayed diagnoses, which may contribute to the disease's aggravation with evolution to sequelae. In Rondônia, about one-third of the patients with PCM had a diagnosis based on clinical-epidemiological criteria<sup>14</sup>, as serological examination was not an available method during this period. In the last 4 years, data on more than 100 PCM cases treated at the Tropical Medicine Center of Rondônia showed a predominance of the chronic form with frequent mucosal involvement. Further, treatment usually began approximately 7 months after infection and persisted until a therapeutic response from both cotrimoxazole and itraconazole was observed. The expansion of the diagnostic network; the standardization and availability of antigens of the different species described to perform serological tests; the training of health professionals, often from other states and still not aware of the regional importance of PCM; and the availability of easy-to-administer medicines by the public authorities, can contribute to a better approach to the disease.



### Criteria for cure

After the diagnosis of PCM has been confirmed, treatment involves long-term regimens with periodic follow-up, usually on an outpatient basis. The duration of therapy should be evaluated according to the cure criteria based on clinical, mycological, radiological, and immunological parameters.

#### Clinical criteria

Cure clinical criteria for PCM include the absence or regression of disease signs and symptoms of the disease, such as the healing of tegumentary lesions, involution of adenomegaly, and stabilization of body weight. The patient's oral lesions subjectively improve after 2 weeks of initial treatment, and after 1 month, there is lesion scarring. In addition, skin lesions also regress after 1 month and lymphadenomegaly occurs between 2 and 3 months. It is common to observe the persistence of residual symptoms or sequelae as a result of lesion scarring and fibrosis. The most commonly observed sequelae occur in the lungs, lymphatic system, adrenals, and CNS. Signs and symptoms resulting from sequelae should be differentiated from the clinical presentation of active disease.

#### Mycological criteria

Negative direct mycological examination in clinical specimens occurs early if treatment is effective. This parameter is more easily verified when examining respiratory secretions. In other materials, such as biopsies or lymph node secretions, fungal assessment is unnecessary because the lesions regress or disappear with treatment.

#### Radiological criteria

Pulmonary opacities, initially of nodular, micronodular, or reticular pattern, and cavitory lesions tend to become linear images, indicating pulmonary lesion scarring and fibrosis. The stabilization of pulmonary radiological image patterns should be analyzed in semiannual chest X-rays (Table 3).

#### Immunological criteria

The most commonly used serological method for detecting antibodies is the DID reaction. An antibody titer is expected to be negative or stabilized at low levels with treatment (undiluted serum or 1:2 dilution). Alternatively, when using counterimmunoelectrophoresis (CIE), stabilization occurs in undiluted serum until a 1:4 dilution. Serological evaluations should be conducted every 6 months, when available.

#### Post-treatment follow-up

The term *definitive cure* can never be applied to patients with PCM because *P. brasiliensis* cannot be eradicated from the organism. Therefore, the aim PCM treatment is to reduce the fungal load in the patient's body, allowing cellular immunity and the balance between parasite and host to recover. After treatment and the observation of cure criteria, patients should undergo outpatient follow-up with routine clinical and serological evaluation. Clinical relapse can be indicated by a positive titer or increase in the DID titer value. Periodic clinical examination with weight control and verification of oral lesion or lymphadenopathy occurrence should be performed for a period of up to 1 year after achieving the cure criteria.

## CONTROL, PREVENTION, CHALLENGES, AND RECOMMENDATIONS

### Control and prevention

Currently, a vaccine to prevent *Paracoccidioides* spp. infection in humans is not available, although promising results have been observed in laboratory animals<sup>109</sup>. Recommendations for the prevention of PCM derive from knowledge of the most obvious infection situations, which occur as a result of aerial exposure to conidia in endemic areas and predisposing risk factors.

In both rural and periurban environments, inhabitants should avoid exposure to dust from soil excavation, earthworks, and plant manipulation. For rural workers and tractor drivers who are constantly exposed to the dense dust, such as those who perform hand-picking, cleaning (sweeping), and coffee sweeping, exposure should be avoided by using well-sealed cabin machines or N95 respirators (not always available). In practice, the replacement of manual coffee sweeping with an oven may have contributed to an observed decrease in PCM incidence among the former coffee regions. Further, children and immunosuppressed individuals are advised to avoid situations of risk in rural areas. In laboratories, the manipulation of fungal isolates should be performed in a safety hood, especially if the cultures are in the mycelium form. For laboratories that routinely handle *Paracoccidioides* spp., pre-exposure and annual serological examination of researchers is recommended to monitor possible fungal infection. Accidents in a research laboratory involving transdermal inoculation of *Paracoccidioides* spp. should be managed by monitoring the presence of antifungal antibodies in the affected person at the time of suspected infection, after 3 months, and after 6 months. Prophylaxis with itraconazole should be administered orally at 200mg/day for 30 days.

Since chronic PCM has been shown to be associated with both smoking and average alcohol consumption<sup>16</sup>, smoking and excessive alcohol consumption (and subsequent malnutrition) should be avoided before and after exposure. Patients immunosuppressed by drugs and/or transplants<sup>20,110</sup> have an increased risk of developing PCM. Since a case report has described the transmission of supra-renal PCM through kidney donation<sup>111</sup>, prior evaluation of organs from donors suspected of having epidemiological antecedents is recommended. Respective donor recipients suspected of having epidemiological antecedents should also be evaluated before and during immunosuppression via a chest radiograph and *Paracoccidioides* spp. antibody test.

### Challenges

In addition to improving the prevalence and incidence rates of PCM, there are a number of new challenges in the management of the disease, such as the registration of cases by compulsory notification and notification through drug access in outpatient and inpatient cases, standardization of serological methods, critical evaluation of antifungal therapies and corticosteroid use, search for new therapeutic approaches for sequelae, the *P. brasiliensis* complex, and the description of a new species of *Paracoccidioides*, *P. lutzii*.

For the clinician, it is important to evaluate the current epidemiological, clinical, diagnostic, and therapeutic impact of the different species on the human disease. For instance, the north and midwest regions have been associated with PCM infections caused by *P. lutzii* because of molecular identification of isolates in these areas<sup>1,5,9</sup> and higher sera reactivity of patients with proven disease in these areas to *P. lutzii* antigen<sup>63,64</sup>.

Although clinical data and therapeutic response are similar for both species (data from Mato Grosso do Sul), little is known about the isolation and molecular identification of the species in patients<sup>8</sup> because mycological and histopathological examinations cannot distinguish these species and molecular tests are not available in routine laboratories<sup>66</sup>.

The following issues remain unanswered: knowledge of the epidemiological-molecular profile of *Paracoccidioides* isolates in Brazil to enhance the clinical-epidemiological diagnosis; characterization of the antigenic profile of the isolates and their correlation with clinical-laboratory data of disease caused by both species<sup>1,7</sup>, including sequelae and response to different drugs, as well as analysis of drug susceptibility<sup>112,113</sup>.

Of great importance to public health is the introduction of simple methods, such as mycological examination, that can serve as the first choice in diagnosis in poor regions. These methods would be especially useful in cases where tuberculosis diagnosis is excluded. However, this requires the joint effort of public agencies and the academic community to develop a serological diagnosis that is universally available for both *P. lutzii* and *P. brasiliensis* infections, with stable antigenic fractions and easily reproducible tests. The international academic community has united the endemic Latin American countries to create the *Latin American Network of Paracoccidioidomycosis* through the Working Group on Paracoccidioidomycosis<sup>114</sup> to overcome these challenges. The dissemination of knowledge collected from clinical-epidemiological, mycological, and serological data in all endemic regions is also a fundamental step for the early diagnosis, treatment, and establishment of comprehensive patient care.

### Recommendations

The following are general recommendations for improving the care of patients with PCM:

1. Institute a compulsory notification of cases with probable and proven PCM;
2. Create a national registry of cases through notification via access to medicine or hospitalization;
3. Enable universal access to itraconazole and cotrimoxazole for treatment of mild to moderate forms;
4. Enable access to lipid formulations of amphotericin in special situations, such as immunosuppression, and to amphotericin B deoxycholate, which has been released for marketing after receiving approval of minimum pharmacological requirements;
5. Structure a basic care network based on clinical-epidemiological, mycological (direct and cultural), and serological diagnosis;

6. Facilitate access to histopathological diagnosis in the absence of mycological diagnosis;
7. Provide stable and reproducible antigens of *P. brasiliensis* and *P. lutzii* in the public health network;
8. Standardize a serological technique for diagnosis and follow-up at the national level;
9. Stimulate the evaluation of the role of corticosteroids in the treatment of patients with intense and/or extensive inflammatory lesions;
10. Enhance the evaluation of antifungal maintenance therapy in immunosuppressed patients according to the degree of immunodepression;
11. Determine the appropriate moment to introduce antiretroviral therapy to AIDS patients, considering the presence of drug interactions and possibility of IRIS, and establishing the parameters for such evaluations;
12. Create a data bank on the distribution of the different species of *Paracoccidioides* in the country to be used in epidemiological diagnoses and to launch multicentric projects with serological tests and typing of isolates with the support of consolidated groups and network projects.

### AUTHORS' CONTRIBUTION

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## DECLARATION OF POTENTIAL CONFLICT OF INTEREST

This statement was taken to consider only the drugs mentioned in this consensus and whose patents have not been lost in the last five years:

Arnaldo Lopes Colombo, Continuing Medical Education: Gilead, MSD, Pfizer, United Medical and Research Grants from Astellas and Pfizer; Flávio Queiroz Telles, Continuing Medical Education: Gilead, MSD, Pfizer, TEVA, United Medical; Maria Aparecida Shikanai Yasuda, Continuing Medical Education: United Medical.

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## Erratum

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