MANAGEMENT OF PULMONARY PARACOCCIDIOIDOMYCOSIS: AN INTEGRATIVE REVIEW

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ABSTRACT

The present study aims to describe the clinical management of pulmonary paracoccidioidomycosis through the literature. The study used as a method the integrative literature review, carried out via the Virtual Health Library (VHL), and through a search in the Medline, Pubmed and Scielo (Scientific Electronic Library Online) databases using the descriptors "Paracoccidioidomycosis", "Diagnosis". For the evaluation of the research problem and its stratification, the PVO strategy was used, and the following strategy was formulated, which can be seen in Chart 1. The aforementioned strategy allowed the following guiding question to be formulated: What is the importance of diagnosing and treating pulmonary paracoccidioidomycosis (PCM)? The standard diagnosis of PCM is visualization in clinical specimens by direct examination or histopathology of characteristic cells with multiple buttons in biological fluids or fungal isolation. As the choice of the drug to be used depends on the clinical form of the disease, clinical follow-up of the patients being treated is necessary and, if it is necessary to adjust the dose of the drug, side effects may also arise, making it necessary to switch to another drug. Finally, even with clinical improvement throughout the treatment, it is necessary to monitor the patient accurately to avoid recurrence of the disease. Fungal diseases in general and especially paracoccidiodomycosis are a public health problem in Latin America.

Keywords: Paracoccidioidomycosis. Fungal Diseases. Diagnosis. Antifungal treatment.

INTRODUCTION

Paracoccidiodomycosis (PCM) is a deep, systemic and progressive mycosis caused by a dimorphic fungus, Paracoccidioides brasiliensis. In infected animal tissue, naturally or experimentally, it presents itself in a spherical form, with a thick refringent membrane, which gives the cell the appearance of a double contour. In culture, using routine media such as Sabouraud's medium, it grows in filamentous form. In special media, it takes on the yeast-like form, presenting as round, budding cells. Dimorphism is reversible, and can change from yeast-like to filamentous and vice versa (Hahn *et al.*, 2022).

This mycosis is endemic in Latin America, with a higher prevalence in Brazil, Venezuela, and Colombia. In Brazil, the states of São Paulo, Rio de Janeiro, Minas Gerais, Paraná, Rio Grande do Sul, Goiás, and Mato Grosso do Sul contribute with the largest casuistry. In the chronic form, it most often affects males. This fact is attributed to the protection conferred by estrogens on adult women (Peçanha-Pietrobom *et al.*, 2023).

Contagion does not occur in the inter-human form. Possibly, the fungus, in saprofitism in soil or vegetables, reaches man directly. The main gateway of P. brasiliensis into the human body is the inhalation of the fungus through the lungs. There are well-documented reports about the cutaneous port of entry. The frequency with which lesions in the digestive tract have been demonstrated also makes one think of the possible acquisition of mycosis by ingestion of the fungus. However, it sometimes occurs in people who have a weakened immune system (due to another disorder or the use of drugs that suppress the immune system) (Thompson *et al.*, 2021).

There are basically two clinical forms: paracoccidioidomycosis-infection, represented by infected individuals who have progressed to spontaneous cure or who harbor P. brasiliensis in latency, both groups with a positive paracoccidioidin test, and paracoccidioidomycosis-disease, which comprises individuals who manifest the clinical and pathological aspects of the infection (Giusiano, 2021).

Active disease is a systemic infection whose classic triad is lesions of the oropharyngeal mucosa, lymph nodes, and lungs. Infected lymph nodes become swollen and may secrete pus that erupts through the skin, although it causes little pain. The most commonly affected lymph nodes are those in the neck and armpits. The liver and spleen can enlarge sometimes causing abdominal pain. Sometimes the symptoms last for a long period, but the infection is rarely fatal. PCM usually involves all organs and systems and has a tendency to spread, resulting in a wide variety of clinical manifestations (Hahn *et al.*, 2022).

Some people with paracoccidioidomycosis develop a chronic lung disorder that causes scar tissue formation (fibrosis) and widespread lung damage (emphysema). When paracoccidioidomycosis occurs in people younger than 30 years of age or in people with HIV infection or AIDS, the infection is more aggressive. It spreads widely, including to the bone marrow and other organs. People have a fever and lose weight. The lymph nodes, liver, and spleen increase in size and anemia arises (Thompson *et al*., 2021).

The present study aims to describe the clinical management of pulmonary paracoccidioidomycosis through the literature.

METHODOLOGY

The present study used as a method the integrative literature review, which according to Galvão (2012), is a construction of a broad analysis of the literature with pre-defined steps, carried out via the Virtual Health Library (VHL), and through a search in the Medline, Pubmed and Scielo (Scientific Electronic Library Online) databases using the crossings of the descriptors "Paracoccidioidomycosis", "Diagnosis". For the evaluation of the research problem and its stratification, the PVO strategy (Population/Problem, Variable/Results and Outcomes/Outcomes) was used, and the following strategy was formulated, which can be seen in Chart 1. The aforementioned strategy allowed the following guiding question to be formulated: What is the importance of diagnosing and treating pulmonary paracoccidioidomycosis? Based on the guiding question, Boolean operators were used to systematize the searches with the following scheme: Paracoccidioidomycosis AND Diagnosis.

Table 1. Research problem stratification following PVO strategy for research formulation.

P Population	People with pulmonary Paracoccidioidomycosis.
V Variables	Pathophysiology and diagnosis.
O Outcomes	Importance of carrying out diagnosis and treatment.

Source: Prepared by the authors.

The following inclusion criteria were used for the selection of articles: articles written in English; published in the last 10 years and that address the diagnosis of pulmonary Paracoccidioidomycosis. With regard to the exclusion criteria, articles that distanced themselves from the central theme of this review and studies that did not present full abstracts in the searched databases were dispensed with.

After the pre-reading and selective reading of the texts, 10 articles were selected (Chart 2), in which an interpretative reading was carried out in order to answer the research

question of this review.

RESULTS AND DISCUSSIONS

From the searches carried out in the databases, a total of 340 articles were found after using the inclusion and exclusion criteria, with a total of 13 articles being selected, 3 in Scielo, 1 in Medline and 9 in Pubmed.

Chart 1 describes the distribution of the articles used according to author/year, title, objective and results.

Chart 2 - Distribution of articles according to author/year, title, objective and results

AUTHOR/YEAR	TITLE	OBJECTIVE	RESULTS
COCIO & MARTINEZ, 2021	*Serological diagnosis of paracoccidioidomycosis using a Paracoccidioides spp. 5lcança5al antigen and the counterimmunoelectrophoresis method.*	To evaluate the Paracoccidioides ID antigen reagent in sera from PCM cases and patients with other diseases	All active PCM sera (n=24) were reactive using counterimmunoelectrophoresis (sensitivity = 100%), including 11 cases of infection by P. brasiliensis sensu stricto and one by P. americana. The commercial antigen showed satisfactory performance and may contribute to the dissemination of the use of serological tests for the diagnosis of PCM.
BRITO *et al.*, 2022	Paracoccidioidomycosis screening diagnosis by FTIR spectroscopy and multivariate analysis	To evaluate a novel strategy for the diagnosis of PCM using blood serum FTIR spectra from 20 PCM patients and 20 healthy subjects.	FTIR spectroscopy and machine learning applied to the analysis of human blood serum samples have shown great potential for the diagnosis of PCM, being a fast and inexpensive alternative to be implemented as a screening technique.
SILVA *et al.*, 2016	Advances and challenges in paracoccidioidomycosis serology caused by Paracoccidioides species complex: an update	To review advances in paracoccidioidomycosis serology in recent years.	The use of gp43 has become restricted because it has recently been discovered that this marker is not identified in infections caused by Paracoccidioides *lutzii*. Therefore, it is necessary to identify new antigens in both species or specific antigens for *P. lutzii to decrease the morbidity and/or mortality associated with PCM*
GIUSIANO, 2021	The Trojan Horse Model in *Paracoccidioides*: A Fantastic Pathway to Survive Infecting Human Cells	It comprises a literature review of the spectrum of tools and mechanisms exhibited by *Paracoccidioides* to overcome phagocytosis, discusses the Trojan horse model and the immunological context in proven models or the possibility that *Paracoccidioides* applies this tool for dissemination to other tissues.	The Trojan mechanism represents an impressive demonstration of the admirable adaptability of the yeast-like pathogenic form of *Paracoccidioides* to harsh conditions, as an accidental fact in the life cycle of this environmental fungus that tries to survive after inhalation.

HAHN *et al*.2022	Paracoccidioidomycosis: Current Status and Future Trends.	It provides a comprehensive and critical overview of immunopathology, laboratory diagnosis, clinical aspects, and current treatment of PCM, highlighting current issues in patient identification, treatment, and follow-up in light of recent taxonomic developments of *Paracoccidioides species* .	Classic PCM diagnostics benefit from culture-based, biochemical, and immunological direct microscopy assays in a general microbiology laboratory practice, providing a generic identification of agents.
HAHN *et al*.2019	*Clinical and epidemiological features of paracoccidioidomycosis due to Paracoccidioides lutzii*	To describe the clinical manifestations of 34 patients with PCM caused by *P. lutzii*, treated over 5 years (2011–2017) at a referral service for systemic mycoses in Mato Grosso, Brazil,	The results of this descriptive study showed no significant clinical or epidemiological differences that could be attributed to the P species. *lutzii.* Regarding cardiovascular mortality, there was marginal significance for premature menopause after considering the follow-up intervals.
MACHADO *et al*., 2022	*Pulmonary and cerebral paracoccidioidomycosis.*	Describe a case of pulmonary and cerebral Paracoccidioidomycosis	The main findings of pulmonary computed tomography in PCM are ground-glass opacities, consolidations, nodules, masses, cavitations, and fibrotic lesions, often in combination. An inverted halo sign was observed in approximately 10% of patients with active infection. On T1- and T2-weighted magnetic resonance imaging, cerebral PCM shows variable hypo- or hyperintense signs with annular impregnation after contrast injection and perilesional edema. Imaging is essential for differential diagnosis and to direct initial patient care
PEÇANHA-PIETROBOM *et al*., 2023	Diagnosis and Treatment of Pulmonary Coccidioidomycosis and Paracoccidioidomycosis	Critical view of the strategies for diagnosis and clinical treatment of BC and PCM.	Learning to recognize their main epidemiological aspects and clinical manifestations is essential for clinicians to be able to include them in the differential diagnosis of lung diseases and avoid late diagnosis.
PEÇANHA *et al*., 2016	Amphotericin B lipid complex in the treatment of severe paracoccidioidomycosis: a case series	To report the experience of a series of patients treated with ABLC	Almost all patients were male (27/28; 96%). The mean age of the patients was 44.7 ± 15.7 years and the median age was 48.5 years (range 4 to 69 years). Most patients came from rural areas (64.3%). Chronic lung disease was present in 14 patients (50%), the acute form in 5 patients (18%), and the chronic disseminated form in 9 patients (32%). Cure was achieved in all 28 patients (100%) using ABLC.

SHIKANAI-YASUDA *et al*., 2017	Brazilian guidelines for the clinical management of paracoccidioidomycosis.	Update the first Brazilian consensus on paracoccidioidomycosis, providing evidence-based recommendations for the management of patients at the bedside. 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.	Discussion of outpatient treatments, severe forms of disease, prevalence of disease among special populations, and resource-scarce settings, a brief review of prevention and control measures, current challenges, and recommendations.
SANTOS *et al*., 2020	Medication association and immunomodulation: An approach in fungal diseases and in particular in the treatment of paracoccidioidomycosis	To present and analyze recently suggested strategies for the treatment of fungi of medical interest, in particular for PCM, such as the use of combinations of protein fractions or killed microorganisms, such as vaccine antigens, and cellular immunotherapy.	New therapeutic alternatives, such as lipids, vitamins, synthetic or natural products, as well as the use of low-level LASER therapy (LLLT) to modulate the host immune response, increasing the efficiency of existing treatments for mycoses of medical interest and in particular for PCM.
RAMOS *et al*., 2020	Thinking in paracoccidioidomycosis: a delayed diagnosis of a neglected tropical disease, case report and review of clinical reports and eco-epidemiologic data from Colombia since the 2000	To report a case of a patient with Chronic Multifocal Paracoccidioidomycosis with long-standing symptoms and a late diagnosis caused by several barriers to 7cancer	Lip biopsy with silver methenamine staining revealed small and large sprouting yeasts that resemble a "sailor's wheel", confirming Chronic Multifocal Paracoccidioidomycosis. He was successfully treated, but subsequently lost follow-up.
THOMPSON *et al*., 2021	Global guideline for the diagnosis and management of the endemic mycoses: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology	Provide up-to-date consensus and practical guidance in clinical decision-making, involving physicians and scientists involved in various aspects of clinical management.	In vitro susceptibility tests and their correlation with clinical response will also need to be further evaluated. Because many diagnostics require the expertise of specialized reference laboratories, improvements in this area would be a welcome step forward and could reduce the time to diagnosis and initiation of treatment.

Source: Prepared by the authors.

Paracoccidioidomycosis can manifest acutely/subacutely in young patients or chronically, especially in adults. The chronic form is more frequent and has an age of 30 to 60 years due to the prolonged incubation period, with multifocal involvement, especially

respiratory and mucocutaneous involvement. Given its heterogeneous nature, this disease is considered a "great imitator" and can be a diagnostic challenge in areas of low endemicity (Ramos *et al*., 2020).

Various diagnostic tests, such as microbiological, immunological, histopathological, and molecular tests can be performed for the diagnosis of PCM. Standard diagnostic methods for PCM are based on microscopic visualization of typical yeast cells by direct mycological or histopathological examinations. This requires the collection of non-blood samples, some of which are difficult to access, such as biopsies of the larynx, lungs, adrenals, lymph nodes, and central nervous system. In addition, the microbiological diagnosis depends on the isolation of the fungus in the crop, whose growth can take a few weeks (de Brito *et al*., 2022).

Serological tests are widely used in the presumptive diagnosis and also in the follow-up of cases of paracoccidioidomycosis (PCM). Currently, double immunodiffusion on agar gel is the most frequently used method to detect serum antibodies to Paracoccidioides spp. Counterimmunoelectrophoresis is an alternative technique to show precipitating antibodies in agarose gel, with higher sensitivity than double immunodiffusion for serological diagnosis of PCM, despite its more restricted use. Detection of anti-Paracoccidioides spp. antibodies in patients' serum requires extraction of the fungal antigen, which must show adequate reactivity to the selected serological test. This antigen must be reactive with antibodies from patients infected with any of the species of the P. brasiliensis and P. lutzii complex, in addition to having low reactivity with sera from other fungal infections (Cocio *et al*., 2021).

Chest X-rays, complete blood count and erythrocyte sedimentation rate (ESR), biochemical tests of the liver (ALT, alkaline phosphatase), evaluation of renal and metabolic function (serum creatinine, Na, K) are also used as possible forms of diagnosis. Imaging tests, such as ultrasound, computed tomography, magnetic resonance imaging (MRI), and scintigraphic mapping, should be performed only when there is clinical suspicion or laboratory results suggestive of organ involvement that cannot be evaluated by physical examination alone (Shikanai-Yasuda *et al*., 2017; Fabris E *et al*., 2014).

The main findings of pulmonary computed tomography in PCM are ground-glass opacities, consolidations, nodules, masses, cavitations, and fibrotic lesions, often in combination. An inverted halo sign was observed in approximately 10% of patients with active infection. On T1- and T2-weighted magnetic resonance imaging, cerebral PCM shows variable hypo- or hyperintense signs with annular impregnation after contrast injection and perilesional edema. Imaging evaluation is essential for differential diagnosis and to direct initial patient care (Machado *et al*., 2022).

The differential diagnosis of mucocutaneous involvement includes other tropical diseases such as mucocutaneous leishmaniasis, sporotrichosis and histoplasmosis; other conditions such as squamous cell carcinoma, T/Nk cell non-Hodgkin's lymphoma, tuberculosis and vasculitis should be considered; in order to reach the clinical diagnosis, the physician can be guided if there is a concomitant presence of mucocutaneous lesions and adenopathies forming a triad of symptoms characteristic of this disease (Ramos *et al*., 2020).

The standard diagnosis of PCM is visualization in clinical specimens by direct examination or histopathology of characteristic cells with multiple buttons in biological fluids or fungal isolation. However, the difficulty of demonstrating the etiological agent of PCM in different clinical specimens, together with the fact that the mycelial growth phase is very slow and confirmation through the reversion of the yeast to the mycelia form is necessary, since it is a dimorphic fungus, makes the use of serological techniques a good option for the diagnosis of PCM (Silva *et al*., 2016; Hahn *et al*., 2019).

The treatment of choice for PCM is itraconazole at a dose of 200 mg per day, and it has been widely used in the treatment of mild and moderate forms of PCM with high efficacy and safety rates. Therefore, currently, this triazole is the treatment of choice for patients with mild to moderate forms of PCM. The duration of treatment can vary from 9 to 18 months, with a mean duration of 12 months, and the patient should always be evaluated by clinical, immunological and radiological criteria. Although co-trimoxazole is fungistatic and requires a longer treatment duration than itraconazole, co-trimoxazole is the second treatment option for patients with mild to moderate forms of PCM. The advantages of co-trimoxazole include wide availability in the public health system in Brazil. Cotrimoxazole intravenous solution may be used in patients with digestive disorders and/or who do not absorb oral medication well. Co-trimoxazole can also be used in contraindications to itraconazole, or in cases of suspected treatment failure or concomitant treatment for tuberculosis (Shikanai-Yasuda *et al*., 2017; Hahn *et al*., 2022).

For severe and disseminated forms of PCM, amphotericin B in deoxycholate or 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 in 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 oral absorption of the drug has been confirmed (Peçanha *et al*., 2016).

As the choice of the drug to be used depends on the clinical form of the disease, it is necessary to follow up the patients who are being treated and, if necessary, adjust the dose of the drug, side effects may also arise, making it necessary to switch to another drug. Finally, even with clinical improvement throughout the treatment, it is essential to monitor the patient accurately to avoid recurrences of the disease. The use of the term "definitive cure" in patients with PCM cannot be applied because treatment does not totally eradicate P. brasiliensis. The treatment aims to reduce the number of fungal cells and allow the recovery of cellular immunity. Therefore, the use of drugs that stimulate the immune system can help reduce treatment time and reduce the challenges encountered in the treatment of these mycoses (Santos *et al*., 2020).

PCM can be considered a neglected disease, as the notification of new cases is not mandatory and there are no treatment policies implemented, requiring early and accurate diagnosis for the prescription of appropriate treatment and prevention of aggravation, death and sequelae.

CONCLUSION

Fungal diseases in general and especially paracoccidiodomycosis are a public health problem in Latin America. One of the important measures that would help to identify the real extent of PCM in these endemic areas, particularly in Brazil, is the compulsory notification of this disease to health authorities, as is required with tuberculosis and AIDS, and the creation of national notification registries via access to medicines. The standard criterion for the diagnosis of PCM is to demonstrate the presence of the fungus as multiple cells sprouting in clinical or tissue specimens. However, serological tests and imaging exams such as CT, MRI and X-rays also play an important role in the diagnosis and evaluation of the disease, in addition to this, the treatment employed depends on the clinical form of the disease and the patient's follow-up should be done in order to adjust and mitigate any side effects that arise, thus avoiding recurrences of the disease.

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