Paracoccidioidomycosis (PCM) is a systemic endemic mycoses with important morbidity and mortality in Latin America, from Mexico to Argentina. The largest number of patients are reported in five countries: Brazil, Venezuela, Colombia, Ecuador and Argentina. Chile is the single South American country without any reported autochthonous case. Worldwide there are cases described within travelers and migrant populations, especially in United States, Italy and Spain. (Figures 1 and 2)

The aetiologic agent of PCM is *Paracoccidioides* spp, a thermally dimorphic fungi exhibiting mycelial form in nature and yeast elements in host tissue. It currently encompasses two species: *Paracoccidioides brasiliensis* (*P. brasiliensis*) and *Paracoccidioides lutzii* (*P. lutzii*). *P. brasiliensis* contains a complex of at least five phylogenetic clusters ranked as the following phylogenetic species: S1a, S1b, PS2, PS3, and PS4. *P. lutzii* has been described in the last decade as a new species found in Central-Western Amazonian region in Brazil. The characterization of *P. lutzii* as a new species was based on phylogenetic and comparative genomics data, recombination analysis, and morphological characteristics.

Figure 2. Worldwide distribution of PCM. Reproduced from Rosa Junior et al.\(^2\)

The habitat of *Paracoccidioides* is not completely understood but its mycelial form has been associated with humid regions, with medium to high rainfall, mild temperatures, nearby rivers and forests or in areas of agricultural crops.\(^8,9\) Besides humans, the fungus was isolated from armadillos, especially *Dasypus novemcinctus* that was considered to main part of its natural reservoirs.\(^10\) More recently, data provided by histopathological, serological or molecular tests suggests that *Paracoccidioides* is able to infect other mammalian species, such as anteaters, dogs, horses, cattle, monkeys, spiny tree porcupine, raccoons, guinea pigs, two-toed sloth and grisons.\(^7\) (Figure 3)

**EPIDEMIOLOGY**

The major risk factor for acquiring infection is a profession or activity related to the management of soil contaminated with the fungus, mainly in agriculture.\(^11,12\) (Figure 4). However, in recent decades, changes in the demographic characteristics and geographical distribution of PCM have been observed due to the rise of urbanization,
replacement of rural workers by machines and reducing of child labor. Otherwise, environmental factors, such as the expansion of settlements, clearing of forests, and replacement of native vegetation by subsistence agriculture may explain the emergence of new geographic areas where PCM became endemic or hyperendemic. In addition, clusters of acute/subacute PCM cases have been associated with the El Niño events in southwest Brazil and Northwest Argentina. Finally, disturbances of soil during hydroelectric plants constructions, deforestation and highway building were responsible for substantial increases in PCM cases reported from Argentina, Paraguay and Brazil.

Figure 3. Spread of *P. brasiliensis* and *P. lutzii*. Pb: *P. brasiliensis*; Pl: *P. lutzii*. Reproduced from: Shikanai et al.

Since PCM is not a compulsory notification disease, we do not have precise data on its incidence. There is a speculation that at least 10 million habitants of endemic areas have been infected by *Paracoccidies* spp. Indeed, a large survey with skin tests performed with the gp43KDa antigen of *P. brasiliensis* conducted in individuals from rural settlements in an endemic area of the southeast of Brazil demonstrated a prevalence rate of 45.8% of infection. The incidence of PCM has been estimated by using data related to the density of patients assisted by different medical centers generating rates of 1-4 cases/100,000 inhabitants per year in geographic areas with stable endemicity, and 9-40 cases/100,000 inhabitants/year in hyperendemic areas in West Amazon Region.
For the vast majority of patients, primary exposition to *Paracoccidioides* spp. is related to episodes of asymptomatic infections followed by an efficient T cell response and contention of the pathogen at the portal of entry. Less than 2% of all infected patients will develop one of the 2 clinical forms of the disease: acute or subacute (juvenile) form and chronic (adult form). The acute form is probably related to the poor control of fungal multiplication in the host immediately after primary infection, followed by a rapid lymphatic and haematogenous dissemination of the agent. In the vast majority of cases (90%) an efficient T response to the agent is established after the primary infection but a quiescent focus persists for long periods of time. In this scenario, the chronic form of disease typically develops after the fourth decade, usually between 30 and 50 years, following the reactivation of the quiescent focus of the infection. Smoking and intake of distilled alcoholic drinks may favor the progression from infection to disease\textsuperscript{12,13,18}.

There is a clear predominance of male patients (13:1) probably due to the effect of estrogen in the transformation of the aspirated conidia into yeast cells and in the modulation of cell immune response, protecting against infection progression. During childhood and after menopause there is no hormonal protection and disease occurs with equal distribution between genders\textsuperscript{12}.

PCM occurrence in immunocompromised patients is rare. Only 136 cases were reported in HIV patients, 36 in solid organ malignances, 12 in hematologic malignances and 9 after solid organ transplant\textsuperscript{19}.
Mortality attributable to PCM ranges between 3% and 5%, with the exception of immunocompromised patients in whom it ranges from 30-40%\textsuperscript{19,20}. The major impact of the disease is related to a high frequency of sequelae with lifetime functional impairment, a finding probably related to the late diagnosis of this condition: 50% of patients will develop pulmonary sequelae, 3% will develop Addison’s disease and 5-40% deficient response of adrenal to stress\textsuperscript{12,21}.

**CLINICAL MANIFESTATIONS**

1. **CHRONIC FORM**

   The lungs are the most common site of infection in this clinical form, affecting 80%-90% of patients, exhibiting non-specific symptoms such as dry or productive cough, dyspnoea, pleuritic pain or hemoptysis that might be accompanied by systemic signs as weight loss, mild pyrexia, and anorexia. Imaging of lung lesions are usually represented by a bilateral reticulonodular infiltrate. Pulmonary computerized tomography may show consolidations, nodules, mass, cavitation and fibrosis can be found. The severity of pulmonary destruction does not correlate with clinical picture once patients present ventilation/perfusion ratio impairment only at the end-stage of the disease\textsuperscript{5,12}.

![Figure 5](image.png)

**Figure 5.** X-ray (A) and CT (B) showing confluent, reticular, and nodular irregular opacities confined to the central area of the lungs ("butterfly wing" pattern). Reproduced from: Rosa Junior et al.\textsuperscript{2}

The combination of chronic pulmonary infection with mucosal involvement is quite common in clinical practice. Mucosal involvement is usually represented by oral superficial ulcers with microgranulation and hemorrhagic pinpoints, pharyngeal or laryngeal lesions seen in 30-70% of patients. Higher rates of oral lesions are reported by medical centers where dentistry is part of the multidisciplinary team. Hyperemia,
swelling, granulomatous infiltrative lesions, ulcerations, infiltrative lesions and vegetating lesions have all been described in different anatomic sites of the upper digestive tract. In rare cases, other mucosal surfaces can be affected, for example the nasal, ocular and genital mucosa \(^9,11,12\).

Cutaneous ulcers are the most prevalent type of skin lesion and may arise from preexisting solid lesions, such as papular, nodular or verrucous lesions, or as a consequence of inflammatory events that occur in response to the presence of the fungal cells in the dermal tissues. The skin involvement is usually reported in 30% of cases \(^9,11,12,21\).

**Figure 6.** Adrenal images from a patient with disseminated paracoccidioidomycosis. (A) Macroscopic images showing signs of bilateral chronic granulomatous adrenitis. (B) Microscopic images showing fungal yeast cells of *P. brasiliensis* with multiple budding, acquiring the typical “steering wheel” aspect (arrow). Reproduced from: Rosa Junior et al.\(^2\)

**Figure 7.** Patients with the acute/subacute (juvenile) form of PCM. A. Masses in supraclavicular, cervical, and submandibular region. B. Lymphadenopathy of PCM, which must be differentiated from hematological diseases, such as lymphoma C and D. Chylous ascites due to lymphatic involvement in abdomen. A and B Reproduced from Shikanai et al.\(^12\)
Fungal involvement of the adrenal glands is documented in up to 90% of the patients submitted to necropsy and is common in asymptomatic patients who have a suboptimal cortisol response to ACTH stimulation (14% to 44%) or even Addison’s disease (3-7%)\textsuperscript{22}. Neuroparacoccidioidomycosis (NPCM) is a rare (5%) and serious clinical complication of the disease, presenting mostly as a cerebral granuloma with focal signs. Of note, NPCM may also occur without any other manifestation of the disease\textsuperscript{12,23}.

2. RESIDUAL FORMS (SEQUELAE)

Residual clinical manifestations after PCM treatment can be devastating and is associated with organ dysfunction. The anatomical and functional changes are a result of chronic inflammatory processes, leading to the accumulation of collagen in fibrosis. The main sequelae related to PCM are mentioned below:

**Respiratory tract:** Despite treatment, chronic PCM may present with new symptoms, such as varying degrees of cough, clear sputum production and dyspnea. Pulmonary fibrosis leading to COPD is a common irreversible sequela of this disease leading to restriction of the patient’s activities of daily living. Pulmonary fibrosis is documented in over 50% of the cases, even after an adequate course of therapy. Eventually 24% of patients will develop cor pulmonale with secondary hypoxemia and pulmonary hypertension\textsuperscript{24}.

**Endocrine system:** Adrenal function may not recover following completion of treatment. 15% to 50% of patients undergoing adrenal evaluation present with a impaired reserve, despite the absence of clinical manifestations, and 3.5% of these patients present with Addison’s disease, which requires daily cortisol replacement therapy throughout one’s life\textsuperscript{22}.

![Figure 8. Sequelae of PCM. A. Orofacial PCM with involvement of the lips. B. Microstomia following orofacial lesion. C. Pulmonary fibrosis. D. Addison’s disease with excess pigmentation and digital clubbing due to chronic hypoxemia. Photos provided by Professor Paulo Peçanha, Federal University of Espirito Santo.](image-url)
Central nervous system: NPCM can be particularly disabling and the risk of motor deficits, epilepsy, hydrocephalus or significantly raised intracranial pressure requiring ventral shunting is high. Dysphonia following vocal cord lesions, laryngeal obstruction necessitating tracheostomy. The disfiguring microstomia following facial lesions are among other sequelae occasionally observed.

DIAGNOSIS

Table 1. Diagnostic methods for PCM

<table>
<thead>
<tr>
<th>Diagnostic methods</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serology (DID, CIE, IIF)</td>
<td>69-100%</td>
<td>80-100%</td>
<td>• correlates with the severity of disease</td>
<td>• No commercial kits available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• monitor criteria of therapeutic response</td>
<td>• No standardization, impairing reproducibility and repetitiveness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• inexpensive</td>
<td>• No validated serological techniques for <em>P. lutzii</em>.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• May be negative in immunosuppressive conditions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Cross-reaction with histoplasmosis and aspergillosis</td>
</tr>
<tr>
<td>Fresh examination/direct microscopy</td>
<td>48-75%,</td>
<td>HIGH</td>
<td>• Immediate results</td>
<td>Requires skilled professionals to read the exam</td>
</tr>
<tr>
<td></td>
<td>worst in sputum</td>
<td></td>
<td>• Samples are easy to obtain</td>
<td>• Micromorphology of <em>P. brasiliensis/P. lutzii</em> pathogens are not distinguished</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Inexpensive</td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td>25-44%</td>
<td>100%</td>
<td>• Provides material for further evaluation of species, antifungal susceptibility and virulence</td>
<td>2–6 weeks of incubation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Biohazard concerns</td>
</tr>
<tr>
<td>Histopathology</td>
<td>65-97%</td>
<td>HIGH</td>
<td>• May help to define the severity of disease (compact granuloma vs. loose granuloma)</td>
<td>Invasive procedure is required for biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Requires skilled professionals</td>
<td>Small forms of <em>Paracoccidioides</em> spp. might be confounded with <em>Histoplasma capsulatum</em> or <em>Cryptococcus neoformans</em></td>
</tr>
<tr>
<td>Molecular Methods (PCR)</td>
<td>HIGH</td>
<td>HIGH</td>
<td>• Provides species identification</td>
<td>Expensive when compared to conventional methods</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Provides diagnosis in biological materials with low burden of infection</td>
<td>Not available for routine diagnosis of PCM</td>
</tr>
<tr>
<td>Specific Antigen detection Gp43KDA e GP70Kda</td>
<td></td>
<td></td>
<td>• Provides diagnosis in immunocompromised patients with negative production of specific antibodies</td>
<td>Expensive when compared to conventional methods</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Provides diagnosis in biological materials with low burden of infection by detecting specific fungal antigens (serum, BAL, CSF)</td>
<td>Not available for routine diagnosis of PCM</td>
</tr>
</tbody>
</table>
The diagnosis of PCM is usually based on the demonstration of fungal elements suggestive of *Paracoccidioides* spp. in clinical samples, either by direct microscopy or histopathology. Serology tests are also useful for the diagnosis and clinical follow up of the patients, but may be negative in patients with immunosuppressive conditions. Most laboratories prefer to use agar gel precipitation tests (double agar gel immunodiffusion – DID) and counter immunoelectrophoresis (CIE). Other assays are only available in research centers, as indirect immunofluorescence (IIF), immunoenzymatic tests (ELISA, magnetic ELISA - MELISA, inhibition ELISA), dot-blotting, and western blotting. PCR based methods and assays for detecting specific *P. brasiliensis* antigens (gp43 and gp70) were developed but are not available for routine labs. Table 1 summarizes the sensitivity, specificity and other relevant characteristics of the main diagnostic tools available for the diagnosis of PCM.

**Clinical management and antifungal treatment**

*P. brasiliensis* and *P. lutzii* are susceptible to most systemic antifungal agents. Decisions about which drug to use are driven by the severity of the disease, the site of the infection, and contraindications due to organ failures, drug interactions or previous exposition and failure to any specific drug. An initial phase of induction therapy with amphotericin B is only required for treating severe and disseminated infection. Patients with mild or moderate clinical presentations of PCM are initially treated with itraconazole or sulfamethoxazole-trimethoprim (cotrim, SMX-TMT), either oral or IV formulation. All patients require a long period of maintenance therapy with itraconazole or SMX-TMT.

It is important to remember that in patients with neuropaaracoccidioidomycosis itraconazole should be avoided. In this scenario, Amphotericin B and SMX-TMT are considered to be the best alternatives. More recently, voriconazole, a second-generation triazole derivative, was found to be as effective as itraconazole in the treatment of PCM, without apparent advantage in terms of safety. In real life, voriconazole has been rarely used and its indication has been restricted to patients with refractory disease and for some difficult to treat cases of NPCM.
Table 2. Most commonly used drugs in patients with paracoccidiodomycosis.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>Average duration</th>
<th>Specificities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>200mg daily <strong>children &lt;30kg and &gt; 5 years, 5 to 10mg/kg/day,</strong></td>
<td>9-18 months</td>
<td>Choice in mild and moderate forms. Do not use when CNS is involved. Erratic GIT absorption, improved by ingestion in a single intake after meal. Check drug interactions</td>
</tr>
<tr>
<td>Sulfamethoxazole-trimethoprim</td>
<td>Trimethoprim (240mg/12h) Children – trimethoprim 8 to 10 mg/kg VO 12/12h</td>
<td>18-24 months</td>
<td>Use in mild and moderate forms. Oral and intravenous formulations available. Increased experience in children. Good alternative for treating NPCM (might require extended period of use).</td>
</tr>
<tr>
<td>Amphotericin B formulations</td>
<td>Deoxycholate 0.5-1mg/kg/day IV</td>
<td>2-4 weeks (until improvement)</td>
<td>Use in severe and disseminated forms. Caution needed re nephrotoxicity and infusion reactions, especially with deoxycholate.</td>
</tr>
<tr>
<td></td>
<td>Lipid formulation 3-5mg/kg/day IV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table adapted from Brazilian Guidelines for the Clinical Management of Paracoccidioidomycosis, 2017

PUBLIC HEALTH NEEDS

PCM still remains a neglected disease that occurs in poor and rural environments. It disproportionately affects low income populations; perpetuates a vicious cycle of the disease, between poverty and inadequate health care and does not receive attention from the developed world. It promotes poverty by causing long-lasting sequelae and devastating impacts on individual work productivity and quality of life and affects patients who frequently ask for medical care very late, when the disease is at an advanced stage.

Some opportunities to reduce Global Disease Burden and improve patient outcomes are:

- Further work on the epidemiological distribution and the ecological niche of this disease with development of risk maps that could facilitate informed public health interventions - for example in travel advice and targeted screening programs.
- Standardisation of diagnostic methods and identification of new serum markers for the diagnosis of PCM.
Invest in health education programs in hyperendemic areas in order to tackle both exposure to the fungus and the delayed presentation of the chronic disease to medical attention.

More research is required to clarify the most clinically and cost-effective treatment, particularly through randomized control trials. Though itraconazole is the first-line recommended drug, it is not currently provided free of charge in Brazil.

Paula Peçanha-Pietrobom, Joshua Griffiths, Arnaldo Lopes Colombo

December 2018

REFERENCES

11. Peçanha, P.M.; Batista Ferreira, M.E.; Massaroni Peçanha, M.A.; Schmidt, E.B.; Lamas de Araújo, M.; Zanotti, R.L.; Potratz, F.F.; Delboni Nunes, N.E.; Gonçalves Ferreira,


