

Paracoccidioidomycosis (Lutz-Splendore-Almeida disease): treatment, duration of treatment, recurrence, paradoxical reaction, prognosis, prophylaxis

Paracoccidioidomicose (doença de Lutz-SPLENDORE-almeida): tratamento, duração do tratamento, recidiva, reação paradoxal, prognóstico, profilaxia

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DOI: 10.5935/2238-3182.20140020

ABSTRACT

Paracoccidioidomycosis, despite being the most important deep mycosis in Latin America, still has many blindspots in terms of its approach, especially in relation to duration of treatment, cure control and prophylaxis. Depending on severity, the following can be used in the treatment: sulfonamides, azoles (itraconazole and ketoconazole), and amphotericin. The prognosis depends on severity, time between onset and diagnosis, and therapy instituted. In mild forms, prognosis is good; in moderate and severe forms, for which there is risk of developing sequelae and death, it is guarded.

Key words: Paracoccidioidomycosis; Mycosis; Paracoccidioides.

RESUMO

A paracoccidioidomicose, apesar de ser a micose profunda mais importante da América Latina, ainda possui muitas lacunas quanto à sua abordagem, especialmente em relação à duração de seu tratamento, controle de cura e profilaxia. Na dependência da sua gravidade podem ser usadas em seu tratamento: sulfas, azólicos (itraconazol e o cetoconazol) e anfotericina. O prognóstico depende da sua gravidade, do tempo para estabelecer o diagnóstico e da terapêutica instituída. Nas formas leves é bom; e nas formas moderadas e graves, em que há risco do desenvolvimento de sequelas e de morte, é reservado.

Palavras-chave: Paracoccidioidomicose; Micose; Paracoccidioides.

INTRODUCTION

Paracoccidioidomycosis (PCM) is the most important existing deep mycosis in Latin America.¹⁻³ It can affect people of all age groups and evolve in the acute-subacute or chronic forms, especially in children-adolescents and adults older than 30 years old, respectively.¹⁻⁸

Its importance relates to the social and economic costs not only from the disease in activity, because individuals in their more productive phase in life are affected, but also because of the determination of sequelae, which represent cause for incapacitation for work.¹⁻³

Knowledge about PCM is still required to unravel relevant aspects of its treatment and prophylaxis.¹⁻¹⁰

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Submitted: 1/16/2014

Approved: 2/10/2014

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TREATMENT

The general measures, non-pharmacological, are very important and characterized by proper diet to promote recovery from malnutrition, if present; and the interruption of smoking and alcoholism, if occurring. The use of parenteral or enteral feeding may be necessary for some situations of serious involvement and the impossibility of using the oral route (OR) for less than seven days of onset of specific therapy.¹⁻⁷

Environmental protection in relation to risks of manipulating dirt with individual protection equipment to prevent air contamination is still a limited indication measure due especially to the ignorance of the real fungus habitat.¹⁻⁴

Pharmacological measures consist of antifungals with effect on *P. brasiliensis*. The choice of the drug to be administered depends on various circumstances such as clinical severity, previous history of therapeutic resistance, gastro-intestinal drug absorption capacity, association with comorbidities, and treatment adherence. *P. brasiliensis* is sensitive to most antifungal drugs, including sulfonamides, azoles (ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole), amphotericin B, and terbinafine.^{1,2,9,10}

Sulfamethoxazole-trimethoprim (SMX-TMP) or itraconazole can be used in the mild or moderate localized forms,^{5-7,9,10} being amphotericin B (or lipid formulation) reserved for the disseminated and severe forms, as in the central nervous system (CNS).^{2,9,10} Another option for use in serious illness, despite the lack of experience, is intravenous voriconazole (IV). Fluconazole and terbinafine, although active against *P. brasiliensis*, have limited clinical data to be used routinely.

The following medicines are available for use:

- **sulfa drugs:** sulfadiazine is effective, however, its oral dosage (OR) of 6/6 hours makes adherence difficult, especially because months to years of continued administration is required (Table 1).

The association SMX-TMP can be administered through OR or IV. The OR administration should be in the form of pills, at a dose of 400-80 or 800-160 mg; or liquid solution, 200-40 or 400-80 mg per 5 mL. Children who cannot swallow pills or capsules can benefit from the oral solution (syrup) or nasogastric or nasoenteric probes of SMX-TMP (10 mg/kg per day, based on the TMP component split at every 12 hours). The IV administration must be at a dose of 400-80 mg per 5 mL per vial diluting one or two or three vials in 125 to 250 or 500 mL of 0.9% NaCl or SGI, respectively, under infusion in 30 to 60 minutes. In a patient under water restriction, the 5 mL ampoule can be diluted with 75 mL of 0.9% NaCl or SGI, at a dose of 800/160 mg every 12 hours. The duration of treatment is, usually, two to three years. Therapeutic efficacy is around 95%. The SMT-TMP can be used exceptionally in severe forms, at a dose of 8 to 10 mg/kg/day of the TMP component divided into three daily doses. The IV infusion should be transformed into OR with the patient's clinical improvement. SMX-TMP is well tolerated, with adverse reactions occurring around 8% of the cases, which rises to 25 to 50% in patients with acquired immunodeficiency syndrome (AIDS). Its most common side effects involve skin (pruritus, rash, necrolysis, and toxic epidermal), the digestive system (nausea, vomiting, increased transaminases), and hematopoietic (thrombocytopenia). It should not be used in the last month of pregnancy or during breastfeeding due to the risk of promoting kernicterus.

SMX-TMP as the drug of choice results from its availability in the Public Health System, low cost, good tolerability, less need for laboratory control in relation to adverse effects, and possibility of administration in children and the elderly through the syrup form that shows good tolerability or via IV on the unavailability of OR.⁹⁻¹¹

- **azole:** itraconazole, ketoconazole, or voriconazole can be used.

Itraconazole is, as well as the SMX-TMP association, the treatment of choice in PCM without serious systemic involvement. It can be administered OR or IV.

Table 1 - Dose adjustments in patients with renal insufficiency

Drug	Dose	Renal insufficiency			After dialysis
		Light	Moderate	Severe	
Sulfametoxazol-Trimetoprim	800-160 mg, 12/12 h, OR	800-160 mg, 12/12 h	400-160 mg, 12/12 h	Do not use	Sustain scheme
Itraconazol	0.2-0.4 g, 24/24 h, OR	0.2-0.4 g/d	0.2-0.4 g/d	0.2-0.4 g/d	Sustain scheme
Cetoconazol	0.2-0.4 g, 12/12 h, OR	0.2-0.4 g/d	0.2-0.4 g/d	0.2-0.4 g/d	Sustain scheme
Anfotericina B	0.25-1.0 mg/kg, 24/24 h, IV	0.25-1.0 mg/kg/d	0.25-1.0 mg/kg/d	0.25-1.0 mg/kg/d	Sustain scheme

The OR dose should be 200 mg/day, from six to 18 months. Children who cannot swallow pills or capsules can benefit from the itraconazole oral solution (5 mg/kg, 24/24 hours). It should not be used during pregnancy or in meningitis (it shows low liquor levels). Its absorption is more intense in fasting; however, the capsule formulation is better absorbed when ingested with food. Its absorption through OR is compromised by the simultaneous use of H2 blockers, omeprazole, or antacids. It shows a wide distribution in human tissues. Its concentration in the CNS is two to 10 times greater than in plasma. It reaches the inguinal bed in the feet in two weeks after having been administered and lasts for 12 months. It is eliminated through bile, urine, and milk. Its main side effects are nausea, vomiting, hypertriglyceridemia, hypokalemia, increase in transaminases and systemic blood pressure, rash, pruritus, headache, tinnitus, feet edema, and rarely heart failure. The suspension of administration may be required in 4% of patients. It is contraindicated during pregnancy, except in the infection without therapeutic alternative, and in concurrent use with astemizole, cisapride, and terfenadine. It potentiates the action of benzodiazepines, phenytoin, indinavir, rifabutin, rifampin, and warfarin. Its therapeutic efficacy is 95%.^{9, 10, 12-18}

Ketoconazole is presented in the form of 200 mg tablets and as lotion or shampoo at 2%. It can be used in systemic extra-meningeal infections in immunosuppressed patients at a dose of 400 mg/day, from six to 18 months or more; and to prevent relapse, at a dose of 600 to 800 mg/day or more for longer or indeterminate time in patients who are unresponsive to the proposed scheme. It is quickly absorbed by OR, with its serum levels reaching a maximum in two hours and being kept suitable for more than 11 hours. Its metabolism is hepatic and its inactive metabolites are excreted mainly through bile. Its absorption is decreased if used with antacid, H2 blockers, omeprazole, and in gastritis, post gastric surgery achlorhydria, pernicious anemia, and AIDS. It is found in sweat and in small concentration in saliva, urine, and CNS. It has a great affinity for inguinal keratin. It presents cross-resistance with other azoles. Its adverse effects occur in 20 and 30% of patients receiving 400 and 800 mg/day, respectively, characterized by: anorexia, decreased libido, skin rash, slightly elevated transaminases, gynecomastia, hepatitis, impotence, nausea, and vomiting. It is quickly depurated if used with rifampin, phenytoin, and isoniazid. Its associa-

tion with terfenadine, astemizole, or cisapride is contraindicated. It is well-tolerated with food or in fractional doses. It should not be used during lactation. It causes teratogenic effects when used in mice. Its prolonged use requires monitoring of liver function, especially in the elderly.^{9, 10, 12-18}

Voriconazole has excellent *in vitro* activity against *P. brasiliensis*, however, there is not enough data on its use in human PCM. It can be administered at a dose of 400 mg, at every 12 hours on the first day of treatment, followed by 200 mg, at every 12 hours. The average treatment duration should be six months. Its therapeutic efficacy is around 90%. The toxicity of voriconazole stems from hepatotoxicity, skin rash due to photosensitivity, and transient visual disturbances. It can be used, exceptionally, in severe forms of PCM, in doses similar to those used in other invasive infections.¹⁵⁻²³

- **amphotericin:** it has several pharmacological presentations and only IV use. Amphotericin B (amphotericin B deoxycholate) is presented in bottles with 50 mg for IV use after dilution in SGI, in slow infusion, for three to five hours or more, in concentrations of not more than 10 mg/mL.

It should be administered at the dose of 0.5 to 1 mg/kg per day, diluted in 50 to 250 mL of SGI, and infused in four to six or more hours, with the first dose under monitoring of vital signs at every 30 minutes to detect any anaphylactic reaction. It should not be given at more than 1.5 mg/kg/day. Low-dose amphotericin B promotes loss of positive ions and small molecules by the fungal cell (fungistatic action). The higher and accumulated doses cause loss of cellular constituents, metabolic changes, and cellular death (fungicidal action). It also has potent immune stimulating humoral and cellular actions, which potentiates antibody production and increases late hypersensitivity reactions. Its nephrotoxic action can be aggravated by simultaneous use of aminoglycosides, cyclosporine, and antihypertensive. Corticosteroids or digitalis aggravate the potassium depletion caused by amphotericin. *In vitro* antagonism between amphotericin B and imidazole is observed.¹⁹⁻²²

Lipid formulations (liposomal, colloidal dispersion, and lipid complex preparations) show mechanisms of action similar to that of conventional amphotericin B, with reduced nephrotoxicity, however, their cost is high. They should not be used as drugs of first choice in the treatment of fungal infections. All preparations are equally effective. The available formulations are: lipid complex amphotericin B (ABLC,

Abelcef); colloidal dispersion amphotericin B (Amphotec); and liposomal amphotericin B (AmBisome) to be administered, respectively: 5 mg/kg/day, in infusion of 2.5 mg/kg/hour; 3 to 4 mg/kg/day, in infusion of 2 mg/kg/hour; and 3 to 5 mg/kg/day, in infusion in 2 hours. They are indicated before: intolerance to conventional amphotericin B; progressive renal failure; and when there is a contraindication to the use of antifungal agents, such as alternative therapy.¹⁹⁻²²

Amphotericin has a low concentration in liquor; aqueous humor; and pleural, pericardial, peritoneal, and synovial fluids. Its biliary concentration can be elevated. The fetal concentration is half of that in the maternal plasma. Its storage in human tissues is lasting (liver, spleen, kidneys), being detected in plasma and urine at the end of treatment, by up to four and eight weeks, respectively. The main excretion is renal and proportionally inverse to creatinine depuration. The lipid formulation can be administered in higher doses with less renal toxicity and reactions to the infusion without being retained in hepatic and renal insufficiencies.

Resistance to amphotericin B is not observed. It causes anorexia, arthralgia, chills, headache, cramps, dyspepsia, weight loss, epigastric pain, anemia, fever, phlebitis, hypotension, nausea, tachypnea, vomiting, cardiac arrest, and death (with rapid IV injection). Its prolonged use can promote arrhythmia, myocarditis, renal toxicity, and hyponatremia. It triggers renal dysfunction that is reversible in the initial two weeks of treatment with ceased or reduced infusion. The irreversible renal failure can occur with total doses over 7 g. Sodium and potassium depletion must be corrected. The lipid formulation reduces renal toxicity and infusion reactions.^{9, 10, 19-21}

The infusion reaction can be prevented or treated with administration of: a) 0.9% NaCl, 500 mL before and after infusion of amphotericin B (provided there are no contraindications); b) paracetamol, 750 mg for 30 minutes before; c) meperidine, 25 to 50 mg, or hydrocortisone 500 mg or promethazine 30 minutes before; d) heparin, 500 U, IV, 30 minutes before. The reactions decrease with slow central vein infusion on alternate days. Discontinuation is unnecessary unless there is a severe reaction. Hemodialysis does not affect its circulating levels. It does not associate with side effects in pregnant women beyond those already described. It can concentrate on fetal tissue. Its administration must be accompanied by the monitoring of creatinine, uremia, potassemia, magnesemia, CBC,

serum oxaloacetic and pyruvic transaminases, and electrocardiogram once or twice a week.^{9, 10}

Changes from IV to OR, when using nasogastric or nasoenteric probes for drugs should be made as soon as there is significant clinical improvement in the patient defined by standardization of systemic blood pressure, decreased ascites, and improved respiratory function and nutritional status, which is observed after 20 to 40 days of its inception. This transition requires care before extensive abdominal injury because the enteric absorption can be impaired due to swelling on the intestinal wall, lesion of abdominal lymph nodes, and fibrosis. In these cases, itraconazole capsules should be avoided due to its erratic oral absorption.¹⁹⁻²¹

Treatment of PCM co-infection with the human immunodeficiency virus/AIDS

PCM is considered an opportunistic infection in AIDS patients in endemic regions, being included as toxoplasmosis and pneumocystis pneumonia, and is among the diseases that should be prevented by prophylactic administration of SMX-TMP.²²

PCM treatment in cancer

There are some reports of increased frequency of neoplasms in PCM endemic regions.^{23,24} The immunosuppression associated with neoplasia and induced neutropenia by neoplasia or antineoplastic therapy can be significantly important for the establishment of PCM. The early recognition of PCM can provide improved chance of a more successful treatment against *P. brasiliensis*.²⁵

PCM treatment in the CNS

The first option for the treatment of neuroparacoccidioidomycosis is the SMZ-TMP association; however, fluconazole and voriconazole show good penetration into the blood-brain barrier. Itraconazole, although its low blood-brain penetration, features some good results in cerebral PCM.²⁶ Amphotericin can also be used with good results. Increased intracranial pressure may also occur in the CNS involvement requiring draining procedures either exterior or in the peritoneum (derivation of external or peritoneal ventricles).

TREATMENT DURATION

The main therapeutic challenges in PCM are its long duration and high frequency of relapses and sequelae; and comorbidities such as simultaneous endemic diseases like tuberculosis, intestinal helminthiasis, and smoking. The duration of treatment depends on the degree of immunosuppression and malnutrition, virulence and inoculum of *P. brasiliensis*, and antifungal used.^{1, 2, 21-33} Clinical cure or apparent cure are more assumed than just cure.

The duration of treatment should be maintained until obtaining the healing criteria involving the following parameters: a) clinical: regression of signs and symptoms, healing of lesions, and involution of lymphadenopathies; b): radiological: stabilization of radiological images; c): immunological: negative double immunodiffusion in agar gel or by membrane and extracellular antigens (MEXO) and recombinant Pb27 used in the ELISA technique.^{31,32} A good response to antifungal treatment is associated with, in general, reduction in serum antibody titers or titer stabilization in values up to 1:2 observed in three serum samples within intervals of two months. Sequelae, however, may complicate the interpretation of the clinical and radiological data. In patients showing negative double diffusion reaction by agar gel before the treatment start, erythrocyte sedimentation normalization should be used for the end of treatment. The erythrocyte sedimentation generally normalizes between four and 11 months before they negatively impact the reaction of double immunodiffusion in agar gel. The serological exam should be performed prior to starting treatment and every six months until its completion and does not constitute isolated criterion for therapeutic ending. The serology should also be requested on suspicion of PCM recurrence.

The use of azoles must be accompanied by evaluation tests for liver function due to the risk of hepatotoxicity. In patients with pulmonary involvement, thorax telerradiography should be performed at the time of diagnosis and for monitoring therapeutic assessments. Thorax CT should be performed on the simultaneity of lung alterations due to tuberculosis or chronic obstructive pulmonary disease and to evaluate pulmonary sequelae; that of abdomen, when abdominal complaints are prevalent; and that of the skull, before CNS involvement.²⁷⁻³⁰

Despite these considerations, the duration of treatment with azoles varies between six and 12 months,

while with SMT-TMP from at least two to three years. In serious PCM with CNS involvement and in immunosuppressed patients (infection by the human immunodeficiency virus, transplant recipients), therapeutic courses of more than two years might be necessary, even when itraconazole is used.

RELAPSE

Relapse occurs in patients with the acute or sub-acute PCM forms. It is observed in the chronic form when treatment is interrupted before its recommended duration. It is observed in fewer than 5%, up to 25%, and in 20 to 30% of patients with chronic PCM that were properly treated with itraconazole, SMT-TMP, and amphotericin B without following therapy with oral medications, respectively.

Patients with immunosuppression have particular risk of relapse (19%) of six times higher than those without immunosuppression.^{32,33}

PARADOXICAL REACTION

Development of acute PCM may occur in immunocompetent patients with fever, weight loss, and draining of persisted lymph nodes despite long periods of treatment; and improves with the use of systemic glucocorticoids. This is a paradoxical reaction and should be considered in the differential diagnosis of the acute form or in patients who remain symptomatic despite proper treatment. They are compared to the immune reconstitution in the inflammatory syndrome observed in AIDS.^{27, 32}

PROGNOSIS

The intensity of involvement in PCM and the time to establish a specific diagnosis and therapy are crucial for its prognosis. The mild forms have good prognosis, while it is reserved in the moderate and severe forms, in which there are risks of the development of sequelae, particularly: fibrosis and pulmonary emphysema, adrenal insufficiency, neurologic lesions, and cutaneous and mucosal fibrosis, which can cause physical and stigmatizing deformities as in leishmaniasis and leprosy. Mortality in children can reach 10% of cases; being lower in adults, however,

the chronic forms present more morbidity due to sequelae, especially, pulmonary.

PROPHYLAXIS

The main measures of PCM prevention originates from the risk of *P. brasiliensis* inoculation through the use of leaves for anal cleaning; and fungus manipulation in research laboratories through its inadvertent penetration through the skin and mucous membranes.

Protection measures towards inoculation in the laboratory consist of: wash the exposed area with soap and water, search for anti *P. brasiliensis* serum antibodies, and administration of itraconazole 200 mg/day until lesions are no longer observed on the likely inoculum site, and regional adenopathy or serological turning by double immunodiffusion reaction in agar gel. Clinical and serological surveillance should remain for another two months. Clinical surveillance becomes unnecessary in the absence of clinical manifestations and maintenance of negative serology. The emergence of paracoccidioidic lesions or serological turning through double immunodiffusion reaction in agar gel indicates antifungal treatment as usual.

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