Review Article

An update on the use of antifungal agents*

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ABSTRACT

We summarize here data regarding the spectrum of action, the pharmacological aspects, the toxicological aspects and the clinical efficacy of liposomal amphotericin B, amphotericin B in colloidal dispersion, amphotericin B lipid complex, voriconazole and caspofungin. We discuss the use of these more recently introduced antifungal agents in terms of their safety, efficiency and cost. We also offer suggestions for the clinical use of these drugs in pulmonary and systemic infections, with an emphasis on the lower toxicity of the lipid formulations of amphotericin B in comparison with conventional medications. In addition, we explore the possibility of using voriconazole as the primary treatment for invasive infections such as aspergillosis, as well as those caused by *Scedosporium* spp. and *Fusarium* spp., together with that of using caspofungin to treat disseminated candidiasis and invasive aspergillosis.

Keywords: Aspergillosis; Lung diseases, fungal/drug therapy; Amphotericin b/administration & dosage; Antifungal agents/drug therapy; Drug therapy, combination

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INTRODUCTION

In clinical practice, there are few drugs used to control the various fungal infections of the respiratory tract. Sulfonamides, which are effective against only a few agents, were the first drugs used in the treatment of patients with systemic mycosis, being first administered around 1940. In the decade that followed, amphotericin B became available. Its antifungal spectrum and efficacy have placed it (and held it) in the position of the drug of choice for the control of visceral and disseminated infections. Although of little use in isolation, 5-fluorocytosine was considered to work in synergy with amphotericin B, especially against cryptococci. The clinical use of azole drugs began in the mid-1970s. Due to their broad spectrum of action, and after the development of cetoconazole, their easy oral administration, these drugs had a great impact on antifungal therapy. In the 1990s, the imidazoles were joined by the triazoles (fluconazole and itraconazole), which presented greater bioavailability and a more intense effect. Voriconazole, a second generation triazole with a broader spectrum of action than the previous azoles, was recently was approved for medical use. Other new derivates, such as posaconazole and ravuconazole, are still awaiting approval. In the last 15 years, lipid formulations of amphotericin B have been developed. In addition, there are two new classes of antifungal agents: the allylamines, represented by terbinafine, with greater use for both skin and nail mycosis; and the echinocandins, of which caspofungin is the most well known in Brazil.

This review includes a presentation of the most recently developed antifungal agents and of the characteristics of the respective drug groups, as well as of the utility of the new drugs in the control of fungal infections of the respiratory tract.

AMPHOTERICIN B

Like nystatin, amphotericin B is a polyenic antibiotic whose structure is macrocyclic and is characterized by divalent carbon atoms arranged in series. Amphotericin B works as a fungicide, combining with ergosterol, a steroid present in the cell membranes of sensitive fungi, altering their permeability and causing the loss of cytoplasmatic constituents. In addition, this effect leads to oxidative injury, resulting in metabolic alterations that are prejudicial to cell survival.[1] To a lesser degree, amphotericin B also combines with the cholesterol in human cell membranes, altering them and causing adverse effects. The spectrum of the etiological agents sensitive to its antifungal effect includes those of the principal endemic mycoses: Paracoccidioides brasiliensis; Histoplasma capsulatum; Coccidioides immitis; Blastomyces dermatitidis; Cryptococcus neoformans var. neoformans; Cryptococcus neoformans var. gattii; and Sporothrix schenckii. Amphotericin B is effective against Candida spp., although a few strains of non-albicans Candida can be resistant. It is also effective against Aspergillus fumigatus, although the sensitivity of other Aspergillus species varies. Varying susceptibility has also been observed in zygomycetes (Mucor and Rhizopus), as well as in Fusarium spp. Certain microorganisms which cause opportunistic fungal infections, such as Trichosporon spp., Pseudallescheria boydii, Cladosporium spp. and Phialophora spp., are generally resistant to amphotericin B.[1]

The conventional amphotericin B formulation for medical use is a combination of amphotericin B and sodium desoxycholate, which is added to make the amphotericin B soluble in water and stabilize the suspension in mycelial form. The intravenous application, in slow infusion, is necessary to obtain useful levels in the blood and tissues. A single daily dose of 1 mg/kg of body weight results in maximum serum concentrations of 1 to 2 µg/ml in the first hour after infusion, and the initial half-life of the formulation is estimated at 24 to 48 hours.

Conventional amphotericin B reaches the highest concentrations in the liver, spleen, kidneys, and lungs.[2] The levels of the circulating fraction, approximately 95% of which bind with proteins, cholesterol, and erythrocytes, decrease slowly. Therefore, it is possible to administer the antibiotic at 48 to 72-h intervals during the treatment consolidation phase. The principal excretion route is renal, although there is also elimination via the hepatobiliar route, and it is presumed that part of the drug is metabolized.[1] Amphotericin B often produces adverse effects due to cellular and tissue toxicity, either at the time of/caused by the infusion or appearing later. The immediate reactions to the infusion result from the liberation of interleukins and prostaglandins, manifesting as fever, chills, tachycardia, high blood pressure, nausea, vomiting, and tachypnea. The intensity of these immediate

reactions varies according to the patient and decreases with further treatment. The late adverse effects are directly related to the cumulative dose of amphotericin B received as well as to patient sensitivity and underlying conditions. The most common are nephrotoxicity and anemia, which require dose correction and the correction of administration intervals, occasionally requiring that the treatment be discontinued. Other adverse reactions include platelet reduction, dyspnea, low blood pressure, cardiac arrhythmia, and neurological toxicity, as well as thrombophlebitis at the site of application.[3]

The clinical use of amphotericin B is limited by the adverse effects and the need for intravenous application. Therefore, the antibiotic is more often used in cases of invasive fungal infections, particularly in immunosuppressed patients, in the disseminated disease forms in immunocompetent patients, in special situations, such as cases of neuromycoses, or in the absence of another efficacious drug. Cases of cryptococosis, aspergillosis, disseminated infections caused by triazole-resistant Candida spp. and infections caused by certain agents of phaeohyphomycosis and of hyalohyphomycosis constitute primary indications for treatment with amphotericin B.

Lipid formulations of amphotericin B

Liposomes and other lipid structures are used as a means of transporting a drug and increase its therapeutic index. Three lipid formulation of amphotericin B are available for medical use: liposomal; colloidal dispersion; and lipid complex. The incorporation of lipids into particles or macromolecules modifies their pharmacokinetics and tissue distribution. The compounds are removed from the circulation by the monocytic-macrophagic system, and amphotericin B is liberated from the lipids inside the cells. When transported by lipids, amphotericin B reaches higher concentrations in the liver and spleen than when the desoxycholate formulation is used. However, the lipid formulations result in lower levels of amphotericin B in the kidneys. This explains the lower nephrotoxicity of the lipid preparations, which are, on the other hand, discretely more hepatotoxic than is the conventional medication.[4] Even patients with renal injury or with anemia induced by amphotericin B desoxycholate might complete the treatment with lipid formulations, typically without aggravating these adverse effects.[5] Therefore, the main benefit of these preparations is the greater safety in terms of cell toxicity in the prolonged use of amphotericin B.

In comparison with conventional medication, lipid formulations have less in vitro effect on yeast and filamentous fungi.[6] In experimental fungal infections, higher doses of the three lipid preparations of lipid amphotericin B are typically needed to equal or surpass the antifungal effect of the conventional medication.[7-9] Most clinical studies, whether open or controlled, have shown that the efficiency of amphotericin B desoxycholate at a dose of 0.6 to 1.5 mg/kg of body weight/day is comparable to that of lipid formulations administrated in three- to six-times greater doses.[10] Due to the high cost of these drugs, patients treated in some medical facilities are given a mixture of amphotericin B desoxycholate and a lipid solution for parenteral nutrition (Intralipid®, Baxter Healthcare, Deerfield, IL, USA; or Lipofundin®, Braun, Melsungen, Germany). This improvised lipid preparation is of equal efficacy and less safety than is conventional amphotericin B, although it can be less nephrotoxic.[11] The main characteristics of the three lipid formulations licensed for medical use are presented below.

Liposomal amphotericin B

Commercialized under the name Ambisome, the liposomal amphotericin B (L-Amb) formulation incorporates the antibiotic into liposomes, lipid microspheres of 55 to 75 nm in diameter, which are prepared with soy lecithin, cholesterol, and distearoyl-phosphatidylglycerol. Doses of 3 mg of amphotericin B/kg of body weight/day are recommended, although a controlled study demonstrated that higher dosages present no advantages over that of 1 mg/kg of body weight/day.[12] Higher doses (up to 10 mg/kg of body weight/day) have been associated with better responses in experimental infections[13] and have occasionally been used in humans. In comparison with other lipid formulations and with the conventional one, L-Amb reaches extremely high maximum serum concentrations (10 to 35 g/ml, after 3 mg/kg). However, most of the amphotericin remains in the liposomes and is probably inactive. The levels found in the lungs of patients treated with L-Amb and

later autopsied suggest that there is less pulmonary distribution of L-Amb than of the conventional formulation.[14] The L-Amb formulation presents lower toxicity (acute and chronic), the lowest of all of the formulations, making rapid infusion and the safe use of doses up to 5 mg/kg/day possible.[4] As to its efficacy, L-Amb was evaluated principally as an empirical treatment for patients with hematological neoplasias. In controlled studies with febrile neutropenic patients, L-Amb showed efficacy superior[15] or equivalent to conventional amphotericin.[16] Patients presenting seropositivity for the human immunodeficiency virus and cryptococcal meningitis demonstrated similar overall responses to the two formulations. However, in such patients, cerebrospinal fluid cultures reach negativity more rapidly when treated with L-Amb than when treated with amphotericin desoxycholate.[17] It has been shown that 54% to 63% of patients with cancer and invasive aspergillosis, most with pulmonary involvement, present a radiological response when medicated with L-Amb.[12] The same formulation evaluated in several types of immunosuppression provided a cure in 59% to 77% of patients with aspergillosis and in 56% to 79% of patients with candidiasis.[18-20]

Amphotericin B in colloidal dispersion

In the amphotericin B in colloidal dispersion (ABCD) formulation (Amphocil®), amphotericin B is contained, together with cholesterol sulphate, in microdiscs with an average diameter of 122 nm. The use of single daily doses of 3 to 4 mg/kg of body weight is suggested. However, ABCD has been used in doses between 1 to 8 mg/kg of body weight/day. The maximum blood levels are lower than or equal to those achieved with the conventional medication, and a pharmacokinetic study in rats also showed low concentrations in lung tissue.[21] Although it is less nephrotoxic, immediate reactions to ABCD are common, and it should therefore be infused slowly. Evaluated as an empirical treatment in febrile neutropenic patients, ABCD has shown an efficacy comparable to that of the conventional formulation.[22] In a controlled study, ABCD proved equally efficient in the treatment of patients with invasive aspergillosis.[23] In open studies, ABCD in immunosuppressed patients resulted in complete or partial response in 57% to 58% of candidiasis cases and in 34% to 39% of aspergillosis cases.[24-25]

Amphotericin B lipid complex

The amphotericin B lipid complex (ABLC) is a macromolecular complex of amphotericin B with dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol, composed of particles in a ribbon-like structure, the ribbons ranging in length from 1.6 m to 11 m (Abelcet®). Adults and children receive the equivalent to 5 mg of amphotericin/kg of body weight/day, a dosage which produces maximum serum concentrations similar to those of amphotericin B desoxycholate. At higher doses of ABLC, the levels in lung tissue might surpass those attained through the use of the conventional drug.[7] The ABLC has no advantage in terms of infusion-related reactions, although it presents lower renal toxicity. When evaluated in patients infected with the human immunodeficiency virus 1 and cryptococcal meningitis, no difference was observed in the percentage of favorable responses between amphotericin desoxycholate and ABLC. However, many patients in the latter group maintained positive culture for cryptococcus at the end of the treatment.[26] In uncontrolled studies of patients with opportunistic infections, ABLC showed an efficacy of 42%, 67% and 100% in aspergillosis cases, of 66%, 67% and 100% in candidiasis cases, of 71% in zygomycosis cases, and of 82% in fusariosis cases.[27-29]

AZOLE DRUGS

Azoles are chemotherapeutic antifungal agents characterized by a pentagonal ring in the molecular structure and divided into two classes: the imidazoles contain three atoms of carbon and two of nitrogen; whereas the triazoles contain two atoms of carbon and three of nitrogen. Considering the systemic drugs, the imidazoles include miconazol and cetoconazole, whereas the triazoles include fluconazole, itraconazole, voriconazole, posaconazole, and ravuconazole. The azoles work on the enzymes of the cytochrome P450 of the fungi, blocking the demethylation of lanosterol and the synthesis of ergosterol, which alters the permeability of the membrane and the fungal viability. They also modify lipid synthesis and inactivate enzymes of the oxidative process of fungi. The azoles, especially the imidazoles, exert only a fungistatic effect. Alterations in the C-14-alpha demethylase enzyme and increased drug efflux are causes of azole

resistance, which has been demonstrated to be particularly common in non-albicans Candida.[30]

All azoles have serum half-lives long enough to make treatment with one or two daily doses possible. Fluconazole has excellent bioavailability, attaining good concentrations in different organic fluids, including in the cerebrospinal fluid, and 75% of the oral dose is excreted in urine. Cetoconazole and itraconazole present less bioavailability, since they depend on gastric pH lower than 3 for their (albeit partial) solubilization and absorption. They do not reach useful levels in the cerebrospinal fluid or urine, being metabolized in the liver and excreted via the biliary route. The concentrations of itraconazole in the liver, lungs, and bones surpass the serum level. The principal adverse effects of the azole drugs are related to gastrointestinal intolerance, hepatotoxicity, and hypersensitivity. Cetoconazole in elevated doses can cause gynecomastia and menstrual irregularities. The azoles are teratogenic drugs and should not be administered to pregnant women. Several drug classes interact with azoles, including those (such as rifampin, isoniazid, phenytoin, phenobarbital, and carbamazepine) that reduce the serum levels of the antifungal agent and those (such as cyclosporine, digoxin, terphenadine, warfarin, benzodiazepines, and human immunodeficiency virus 1 protease inhibitors) that elevate the levels of other drugs.[30]

The spectrum of agents against which the imidazoles and triazoles are effective encompasses those of paracoccidioidomycosis, histoplasmosis, coccidioidomycosis, cryptococosis, North American blastomycosis, and dermatomycosis. The majority of Candida species present susceptibility to azoles, although C. krusei and C. glabrata are less so. Itraconazole is also effective against A. fumigatus and several other species of this genus, being an alternative to amphotericin in the treatment of patients with aspergillosis, as well as being the main resource in antifungal therapy for patients with endemic systemic mycoses. Cetoconazole is also used in the control of endemic systemic mycoses, although its use is restricted to mild cases. Fluconazole works well and is preferred in the treatment of patients with infections caused by sensitive species of Candida, as well as being used against cryptococosis, urinary infections, and central nervous system infections caused by susceptible fungi. Voriconazole, posaconazole and ravuconazole are second-generation triazoles, created by modifying the chemical structure of fluconazole and itraconazole. They represent advances in the therapeutics of fungal infections for they have a widened spectrum of action.[31] Voriconazole, now available for medical use under the name V Fend®, is presented below.

Voriconazole

This drug maintains the general properties of the azoles. However, it presents more pronounced blockage of ergosterol synthesis in the filamentous fungi, for which it acts as a fungicide. It has a more intense in vitro effect on Aspergillus species, including A. terreus, which is commonly resistant to amphotericin B, than does itraconazole. It is effective against many species of Fusarium, Paecilomyces, Alternaria, and Bipolaris, as well as against Scedosporium apiospermum and P. boydii. It is fungistatic for Candida species (including those resistant to fluconazole), Cryptococcus spp., and Trichosporon spp. and is also effective against fungi that cause endemic mycoses.[31-32]

Voriconazole is administered orally or intravenously in a dosage of 6 mg/kg of body weight every twelve hours on the first day and 4 mg/kg of body weight every twelve hours thereafter. Adults receive oral doses of 200 mg (in tablet form) every twelve hours (100 mg every twelve hours for patients weighing less than 40 kg), which makes it possible to reach a maximum serum concentration of 4 to 6 µg/ml in a state of equilibrium.[33] Absorption does not depend on gastric acidity, and the bioavailability of the oral drug is good. Voriconazole reaches levels inhibitory for fungi in the encephalon and in the cerebrospinal fluid. Because it is metabolized and excreted by the liver, it is necessary to adjust the dosage or avoid its use in cases of hepatic insufficiency. In cases of moderate to severe renal insufficiency, intravenous administration is contraindicated due to the risk of accumulation of the vehicle cyclodextrin.[32] Adverse effects are common but usually benign. In addition to those effects common to the azoles, approximately 30% of patients present visual disturbances - altered color discrimination, blurred vision, photophobia - in the first week of treatment, symptoms which attenuate and then disappear. Hypersensitivity reactions, from discrete exanthemas to severe reactions, have also been reported. In clinical practice, voriconazole has been employed principally in infections caused by

Aspergillus spp. and other opportunistic fungi. A randomized study of patients with invasive pulmonary aspergillosis demonstrated the superiority of this triazole over amphotericin B, in relation to favorable responses and to survival.[34] In open studies of immunosuppressed patients and patients with invasive aspergillosis, complete or partial response to primary treatment with voriconazole was observed in 59%[35] and 66%[36] of patients, results considered equivalent to or better than those seen in historical controls. In cases of candidemia in non-neutropenic patients, a randomized study showed comparable efficacy between voriconazole and amphotericin B desoxycholate.[37] A similar result was observed between two medications in the percentage of success in the empirical treatment of patients with neutropenia and persistent fever.[38] Voriconazole constitutes an important therapeutic resource in certain infections caused by fungi commonly resistant to amphotericin B, as in the case of Scedosporium spp. and P. boydii.[36,39] However, some species or strains of opportunistic fungi are resistant.[39]

ECHINOCANDINS

Echinocandins are semi-synthetic lipopeptides with a chemical structure of cyclic hexapeptides connected to a lateral chain of fatty acid. Three drugs - caspofungin, micafungin, anidulafungin - have reached the clinical investigation phase, and caspofungin has been licensed for clinical use (Cancidas®). Unlike amphotericin B and the azoles, the echinocandins target the cell walls, inhibiting the enzyme linked to the synthesis of beta (1.3) D glucan.[40] Glucan in the form of microfibrils is one of the main components of the fungal cell wall. The blocking of its synthesis results in osmotic imbalance, damaging the viability of the microorganism. Echinocandins is effective against various yeasts and filamentous fungi in vitro, however in experimental infections only its activity on Candida and Aspergillus species is relevant. For this latter agent, it is only fungistatic.[31,41] The adverse effects are less frequent than with amphotericin B and the interaction with other medications is smaller than with the azoles. However, the exclusive intravenous administration and the restricted spectrum of effect limit the clinical use of echinocandins to more severe infections caused by Candida and Aspergillus.

Caspofungin

Caspofungin is a semi-synthetic derivate of pneumocandin B, a natural product of Glarea lozoyensis. It has a fungicide effect on various Candida species, including strains resistant to fluconazole and amphotericin B. C. guilliermondii is less sensitive, and caspofungin has only a fungistatic effect on some strains of this species. Caspofungin in concentrations similar to those attained in patient plasma have been shown to inhibit the majority of the different Aspergillus species, including those resistant to itraconazole.[41] The minimal inhibitory concentrations are greater for A. terreus and A. nidulans.

Caspofungin is administrated intravenously at one-hour intervals. Since it has not been sufficiently evaluated in children, it is recommended only for adults, who receive doses of 70 mg dose on the first day and 50 mg on the subsequent days. With this treatment regimen, the average serum concentrations of the drug are higher than 1 µg/ml, sufficient for the inhibition of Candida and Aspergillus. In patients with moderate hepatic insufficiency, the dose should be reduced to 35 mg/day. However, the daily dose should be maintained at 70 mg, when metabolism inductive medications are simultaneously administrated, such as rifampin, efavirenz, nevirapine, dexamethasone, phenytoin, and carbamazepine. Studies in animals suggest preferential distribution of caspofungin to the liver and reduced levels in the encephalon. The drug is excreted via the urinary and hepatic routes after being hydrolyzed and acetylated. It should not be administrated in conjunction with cyclosporine, since the latter inhibits the hepatic uptake and raises the levels of the antifungal agent.[40]

Caspofungin might occasionally cause reactions during infusion, since its polypeptide structure facilitates the appearance of symptoms secondary to histamine liberation. Other adverse effects, such as fever, migraine headache, nausea, vomiting, eosinophilia, elevation of hepatic enzymes, and thrombophlebitis, have been observed. In the treatment of oropharyngeal or esophageal candidiasis, caspofungin showed efficacy comparable to that of conventional amphotericin B[42] and of fluconazole.[43] The therapeutic success was also comparable between conventional amphotericin B and echinocandin in cases of candidemia and peritonitis caused by several Candida species.[44] In a study of invasive aspergillosis,

a favorable response to caspofungin was observed in 45% of patients, higher than the 17% obtained in historic controls.[45] A randomized study of patients with febrile neutropenia showed a favorable response to caspofungin and to liposomal amphotericin B in 34%.[46]

CLINICAL USE OF NEW ANTIFUNGAL AGENTS

Lipid formulations of amphotericin B

Despite the fact that it has been used continuously for decades, amphotericin B remains the gold standard for systemic antifungal therapy. It works rapidly and causes lethal damage to the majority of agents of opportunistic and endemic mycoses, few of which have developed amphotericin B resistance. The lipid formulations of amphotericin B were designed to make it less toxic, thereby allowing the administration of higher daily doses and increasing its efficiency. The clinical use of these lipid amphotericins, replacing the traditional desoxycholate formulation, is currently being analyzed in terms of efficacy, safety, and cost.

Randomized clinical trials have generally shown that the efficacy of conventional amphotericin B is equivalent to that achieved with lipid formulations, particularly in cases in which fungal etiological agent is identified. With the exception of histoplasmosis, in which liposomal amphotericin B has been shown to provide a greater percentage of favorable responses,[47] the efficacy of the new formulations is similar to that of conventional amphotericin B in patients with cryptococosis,[17,26] candidiasis,[10] aspergillosis,[23] or (empirical treatment of) neutropenia with persistent fever.[16,22] Notwithstanding these observations, it is accepted that one of the indications for the use of lipid preparations is presumed failure of amphotericin B desoxycholate treatment, using the criterion of the lack of a favorable response after an accumulated dose of 500 mg.[48] In that case, it is supposed that the fungus is susceptible and, especially in the empirical treatment of immunosuppressed patients, daily doses greater than those recommended for conventional amphotericin B but within the therapeutic range recommended for L-Amb, ABCD and ABLC, are used.

There are not a sufficient number of controlled studies in order to compare and distinguish among the three lipid formulations in terms of their clinical efficacy and systemic effect.[49] Each formulation has specific pharmacokinetic and pharmacodynamic characteristics that differ from those of amphotericin B desoxycholate, which might imply different responses in the infection control in certain organs and systems. The L-Amb, ABCD and ABLC formulations accumulate in the liver and spleen to a greater degree than does the conventional formulation. Apparently, this represents an advantage in the fight against sensitive microorganisms which lodge preferably in the monocytic-macrophagic (reticulo-endothelial) system cells, as in cases of histoplasma and leishmania. In other organs, however, the levels of amphotericin B produced by the lipid formulations are, apparently, lower than or equal to those attained with the conventional formulation, with the exception of L-Amb, which produces central nervous system concentrations equal to or higher than those attained with the conventional drug.[10] Despite the scarcity of information on the pharmacodynamics of the lipid-vehicle medications in humans, some available evidence suggests that the concentration of amphotericin B distributed in the lungs is no higher than that obtained with the conventional medication. Some experimental studies[7,50] and some clinical studies[51] have demonstrated lower capacity of lipid amphotericin B in the control of fungal infections of the respiratory tract. On the other hand, several clinical investigations, randomized or open, demonstrated the efficacy of such formulations. Clinically, the three lipid preparations are considered similarly effective and that they do not clearly surpass conventional amphotericin B as an initial treatment for fungal infections of the respiratory tract.[49]

The greatest motivation for the therapeutic use of the lipid formulations results from their proven lower nephrotoxicity. The L-Amb formulation has the additional benefit of low incidence of immediate effects after infusion. The elevated cost of these medications, however, limits their routine use considerably. Their administration is most commonly indicated when the patient requires amphotericin B as the most suitable antifungal agent but presents persistent serum levels of creatinine above the 2.5 to 3.0 mg/dL range, despite the measures taken to reduce the nephrotoxicity of amphotericin B desoxycholate, such as reducing the daily dose to the 0.3 to 0.4 mg/kg of body weight range. Patients

Chart 1 - Antifungal therapy for adults with pulmonary and systemic mycoses

Fungal infection / clinical form	Primary therapy	Therapeutic alternatives	Observations
PARACOCCIDIOIDOMYCOSIS	Itra: 400mg/d (6m - 18m)* or	Ceto (400mg/d)	Vorico = Itra in clinical
Pulmonary, oral, or of the laryngeal mucosa	SMX + TMP: 2400 - 480mg/d →1600 - 320mg/d (12m - 24m)*	Fluco (400mg/d)	Failure of Amph B-l (ABCD)
Disseminated, severe cases	Amph B-d (t dose = 35mg/kg) →Itra: 400mg/d (≥ 18m)*	Itra, Fluco, Ceto	
HISTOPLASMOSIS			
Pulmonary, acute, severe, or prolonged	Itra - 400mg/d (6 - 12 sem)	Amph B-d (t dose = 20mg/kg) →itra (12 wk)	Corticoid therapy, if respiratory insufficiency
Pulmonary chronic; mild disseminated	Itra - 400mg/d (12 - 24 m)	Amph B-d (t dose = 20 - 35mg/kg) →itra (12 - 24 m)	Other alternatives: Ceto, Fluco, SMX-TMP
Disseminated severe, immunosuppressed	Amph B-d (t dose > 35mg/kg) →Itra = 400mg/d (≥ 24 m)	Itra (400 - 600mg/d)	Lower mortality with Amph B-l (L-Amb) x Amph B-d
COCCIDIOIDOMYCOSIS			
Pulmonary acute diffuse	Amph B-d (t dose = 20 - 35mg/kg)	Itra, Ceto, Fluco	Corticoid therapy, if respiratory insufficiency
Disseminated	Itra (400mg/d) (≥ 12 m)		
Pulmonary, chronic fibrocavitary	Itra - 400mg/d (12 m)	Ceto - 400mg/d, Fluco - 400mg/d, Anf B-d	Consider surgery in cavitary process
ASPERGILLOSIS			
Aspergilloma	Itra - 400mg/d (≥ 12 m)	Amph B-d (35mg/kg)→ Itra (≥ 12m)	Consider surgical removal
Bronchopulmonary allergic	Itra - 200mg/d (4 m)		Combine corticosteroid
Pulmonary necrotizing chronic/fibrosing	Itra - 400mg/d (≥ 12 m)	Amph B-d (35mg/kg)→ Itra (≥ 12m)	
Invasive	Amph B-d (Amph B-l) or Vorico - 4mg/d, IV	Caspo - 70→50mg/d Itra - 400 a 600mg/d	Consider surgical removal ↓immunosuppression
CRIPTOCOCOSE			
Pleuropulmonar localizada, em imunocompetentes	Fluco = 200 - 400mg/d (3 - 12 m)	Amph B-d (t dose = 20 - 35mg/kg)	
Disseminada, meningite, imunossuprimidos	Anf B-d: 0,7 - 1mg/kg/d + 5FC: 100mg/kg/d (2 sem)→Fluco: 400-800mg/d (10 sem)→Fluco: 200mg/d (≥6m)	Amph B-d (t dose = > 35mg/kg→ Fluco - 200mg/d (> 6m)	L-Amb - 4mg/kg/d Amph Bd in efficacy

Continua

Continuação

CANDIDIASIS			
Pulmonary, aspiration	Amph B-d (t dose > 20mg/kg	Fluco: 6 - 12mg/kg/d	*C. krusei* and *C.glabrata* less sensitive to Fluco
Pulmonary, hematogenic, or candidemia	Fluco: 6 - 12mg/kg/d or Amph B-d: 0,7 - 1mg/kg/d (> 14 days after last + culture)	Amph B-l or Caspo: 70 50mg/d	*C. guilliermondii* less sensitive to Caspo
(ZYGO) MUCORMYCOSIS			
Pulmonary, invasive, disseminated	Amph B-d (t dose > 35mg/kg)	Amph B-l	Posaconazole works in vitro
SPOROTRICOSIS			
Pulmonary, disseminated	Amph B-d (t dose > 35mg/kg) Itra - 400mg/d (3 - 6 m)	Itra: 400 - 600mg/d (6 - 12 m)	
FUSARIOSIS			
Pulmonary, invasive, disseminated	Amph B-d (t dose > 30 - 35mg/kg) or Vorico - 400mg/d, IV	Amph B-l	Species of Fusarium: variable sensitivity
SCEDOSPORIOSIS/PSEUDALLESCHERIASIS			
Pulmonary, disseminated	Vorico - 400mg/d, IV	Amph B-d or Amph B-l	*S. prolificans* less sensitive to Vorico
PHAEOHYPHOMYCOSIS, pulmonary *Bipolaris, Exophiala, Exserohilum, Phialophora, Wangiella spp., etc.*	Amph B-d (t dose > 35mg/kg or Vorico - 400mg/d, IV	Amph B-l; Itra: 400 - 600mg/d	Consider surgery
HYALOHYPHOMYCOSIS, pulmonary *Paecylomices, Acremonium, Scopulariopsis spp., etc.*	Amph B-d (t dose > 35mg/kg) or Vorico - 400mg/d, IV	Amph B-l; Itra: 400 - 600mg/d	Uncertain fungal sensitivity
TRICHOSPORONOSIS, disseminated *Trichosporon* spp.	Fluco: 400 - 600mg/d (IV OR)	Vorico, Itra, Amph Bd	Generally resistant to Amph B
Neutropenia and persistent fever Possible fungal infection	Amph B-d (Amph B-l)	Itra, Fluco, Vorico or Caspo	Individualize treatment

Itra: itraconazole; SMX-TMP: sulfamethoxazole-trimethoprim; (g): treatment sequence; Amph B-d: amphotericin B desoxycholate (conventional); t dose: total dose; Ceto: cetoconazole; Fluco: fluconazole; Vorico: voriconazole; Amph B-l: lipid formulation of amphotericin B (liposomal - L-Amb; in colloidal dispersion - ABCD; or lipid complex - ABLC); Caspo: caspofungin; IV: intravenous; OR: oral

* Variable period of treatment, according to case severity; patients who do not meet the clinical and laboratory testing criteria for cure, or immunosuppressed patients, might require antifungal therapy regimens of longer durations.

presenting a strong reaction to the infusion of the conventional drug that is not controlled with premedication or by decreasing the rate of administration will also benefit from its replacement by L-Amb. In cases of sequential use of the lipid formulations to attenuate or avoid the adverse effects of conventional amphotericin B, the total dose remains the same, since the amount already administered is computed. At the time of replacement due to the occurrence of adverse effects, patients already in clinical recovery might maintain a good response, even with a daily dose of lipid amphotericin B equal to that of the conventional drug.[5]

Azoles and echinocandins

Azole drugs and echinocandins are equally used in the primary treatment of systemic fungal infections or, secondarily, after the failure of or intolerance to amphotericin B desoxycholate. The selection of the antifungal agents takes into special consideration the susceptibility of the probable or identified causal agent, the existence of oral and intravenous preparations, medication interactions, and the cost of the treatment.[52] Since they are expensive, voriconazole and caspofungin are commonly reserved for the treatment of severe infections or of infections that do not respond to other antifungal agents. Mild pulmonary infections caused by filamentous or dimorphic fungi are usually treated with itraconazole when the etiological agent is sensitive to this drug. Cetoconazole is an alternative to itraconazole, although it presents lower bioavailability and efficacy. Invasive aspergillosis, fusariosis, and scedosporiosis might be more efficiently controlled with voriconazole or, in treatment-naïve patients, caspofungin. For infections caused by susceptible Candida species and other yeasts, fluconazole is an antifungal agent of renowned efficacy and medium cost. In infectious processes caused by Candida spp. that are resistant to fluconazole and amphotericin B, as well as for patients that are intolerant to these medications, caspofungin or another echinocandin is used.[53] Chart 1 summarizes the principal therapeutic options for the most common endemic and opportunistic fungal infections in Brazil.[53-59]

Combination antifungal therapy

In treating patients with a combination of two or more antifungal agents, except under certain conditions, care must be taken in order to avoid the possibility of antagonism between the drugs. The combination of amphotericin B and 5-fluorocytosine presents synergy and is the initial treatment for cryptococosis and in certain cases of candidiasis and aspergillosis. The same effect was evidenced for fluconazole and 5-fluorocytosine in cryptococosis and candidiasis. However, the combination of amphotericin B and azole drugs might result in lower efficacy than that of amphotericin B in isolated use or, simply, in the absence of synergism. In general, the combined use of itraconazole or other azoles and amphotericin B is avoided, and, if possible, the use of amphotericin B in sequence to a therapeutic course with itraconazole or other azoles is also avoided. Terbinafine, echinocandins, and voriconazole are being investigated in combination with one another and with traditional antifungal agents in infections produced in animals, as well as, experimentally, in patients with severe fungal infections. The results have varied, and it has not yet been possible to clearly make other associations with the synergistic effect on the efficacy of antifungal agents.[60]

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