REVIEW

Therapeutic armamentarium against systemic fungal infections

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ABSTRACT

The incidence of invasive fungal infections (IFIs) has been following an upward trend over time, due to a continuous increase in the number of patients at risk, while the prognosis remains poor. In the last 10 years, the lipidic formulations of amphotericin B, voriconazole and a new family of antifungal drugs, the echinocandins, have been added to the traditional antifungal agents, for decades limited to just a few drugs such as amphotericin B deoxycholate, flucytosine and, later, fluconazole and itraconazole. These additions have improved both the results and the understanding of antifungal therapy, while at the same time making it more complex, with new questions arising that remain to be answered. This article reviews the mechanisms of action, spectrum of activity, pharmacology, administration, adverse effects and indications of each of the antifungal agents currently commercialised for the treatment of IFI.

Keywords Amphotericin B, antifungal therapy, caspofungin, fluconazole, flucytosine, itraconazole, voriconazole

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CLASSIFICATION

Nine systemic antifungal drugs belonging to four families have been approved for the treatment of invasive fungal infections (IFIs). Table 1 shows the classification of these systemic antifungal agents and their mechanisms of action.

AMPHOTERICIN B DEOXYCHOLATE

Amphotericin B deoxycholate is a natural polyenic antibiotic obtained from *Streptomyces nodosus*. It is usually combined with a deoxycholate suspension in order to achieve the solubility needed for its parenteral administration. It binds ergosterol, which is the main component in the fungal cell membrane, and increases fungal permeability, thus causing cell death. Amphotericin B deoxycholate also acts by means of oxidative mechanisms damaging the cell membrane.

Since the standardised and reliable determination of amphotericin B activity in the different species of pathogenic fungi is not yet definitive, the results of the available susceptibility studies should be evaluated cautiously. The amphotericin B deoxycholate spectrum of action includes the majority of fungi that are pathogenic for humans: *Aspergillus* spp., *Candida* spp., *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides brasilensis*, *Histoplasma capsulatum* and *Penicillium marneffei*. It is also active against the mucormycosis, hyalohyphomycosis and phaeohyphomycosis agents. Resistance to amphotericin B deoxycholate is infrequent and limited to some isolates of *Candida lusitaniae*, *Candida glabrata*, *Candida guilliermondii*, *Aspergillus terreus*, *Scedosporium apiospermun*, *Scedosporium prolificans*, *Fusarium* spp. and *Trichosporon* spp. [1,2]. The mechanism by which *Candida lusitaniae* develops resistance to amphotericin B deoxycholate is a decrease in the synthesis of ergosterol in its membrane [3]. This mechanism of resistance could explain why the susceptibility of *Candida albicans* to amphotericin B deoxycholate decreases after the strain has been exposed to fluconazole [4]. The spectrum of activity of amphotericin B is the same for the different formulations.

Amphotericin B deoxycholate is fungicidal, has a concentration-dependent activity and shows a prolonged post-antibiotic effect (PAE) according to some experimental studies [5]. Its pharmacokinetic profile is complex and has not been sufficiently studied. It binds to plasma proteins 95% of

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Table 1. Classification of the systemic antifungal agents available and their mechanisms of action

Families	Compounds	Mechanisms of action
Polyene antibiotics	Amphotericin B deoxycholate	Binds to ergosterol + oxidative damage to fungal cells
	Lipid formulations of amphotericin B: Amphotericin B lipid complex Amphotericin B colloidal dispersion Liposomal amphotericin B	
Pyrimidines	Flucytosine	Inhibition of DNA synthesis
Azoles	Fluconazole Itraconazole Voriconazole	Inhibition of ergosterol synthesis
Echinocandins	Caspofungin	Inhibition of glucan synthesis

the time and involves the liver, spleen, bone marrow, kidneys and lungs. In spite of the fact that amphotericin B deoxycholate barely crosses the meningeal membrane when this is inflamed, it is active in cryptococcal meningitis. Plasma clearance is slow, although slightly faster in children, and its terminal half-life is 5 days. Most of the drug is degraded in tissue, with only a small percentage being eliminated in urine or bile. Dose adjustment is not required in cases of hepatic or renal impairment or in haemodialysis. Amphotericin B deoxycholate is the only systemic antifungal agent that is not contraindicated during pregnancy [1]. The most frequent adverse effects of amphotericin B are those related to infusion and nephrotoxicity. Half of the patients receiving amphotericin B deoxycholate suffer adverse effects related to infusion, e.g., fever, chills, shivering, myalgia and/or nausea. These effects mainly occur with the first dose administered; however, with subsequent doses, with pre-medication (hydrocortisone 0.5 mg/kg or acetaminophen 10 mg/kg) and with a reduction in the infusion rate, their intensity progressively decreases and they finally disappear. Nephrotoxicity, defined as a two-fold increase in the baseline levels of creatinine, occurs in 30% of patients treated with amphotericin B deoxycholate [6]. It induces vasoconstriction in the renal afferent arteriole and an imbalance in tubular permeability, thereby causing a reduction in the glomerular filtration rate, tubular acidosis and loss of potassium and magnesium. Nephrotoxicity usually stabilises during the course of the treatment and is reversed when the treatment is finished. The risk of nephrotoxicity increases with the total accumulated dose of amphotericin B deoxycholate, male sex, previous renal impairment and high co-morbidity. Patients developing renal failure during treatment with amphotericin B deoxycholate show higher mortality rates [6]. The administration of physiological saline solution reduces the risk of nephrotoxicity associated with amphotericin B deoxycholate [7].

It has recently been demonstrated that administration of amphotericin B deoxycholate by slow, continuous intravenous infusion (over 24 h or at a rate of infusion <0.08 mg/kg/h) is associated with a lower incidence of adverse effects related to nephrotoxicity and infusion when compared with the usual administration over 4 h [8]. This beneficial effect has also been demonstrated in patients who have received allogeneic haemopoietic stem-cell transplants (HSCTs) and in those receiving simultaneous treatment with other nephrotoxic drugs [9]. The administration of amphotericin B deoxycholate as a continuous infusion allows amphotericin B doses of up to 2 mg/kg/day, with no additional toxicity [10]. The efficacy of amphotericin B deoxycholate administered by continuous infusion is, however, still under discussion, since, according to experimental data, its antifungal activity is concentration-dependent. However, according to both of these studies, amphotericin B deoxycholate administered by continuous infusion reduces overall mortality as compared with administration at the standard rate [8,9].

The main interactive effect of amphotericin B deoxycholate is an increase in the plasma levels of those drugs that undergo renal elimination, since it reduces glomerular filtration. Co-administration of neutrophils and amphotericin B deoxycholate is associated with severe acute pulmonary damage [1].

Amphotericin B deoxycholate remains the antifungal agent of choice against many IFIs,

including invasive candidiasis, cryptococcosis, mucormycosis, histoplasmosis, blastomycosis, coccidioidomycosis, penicillosis, sporotrichosis and phaeohyphomycosis. The amphotericin B deoxycholate dosage depends on the type of infection, the species and the host factors. The dose recommended for invasive candidiasis is: 0.6 mg/kg/day for infections caused by *Candida albicans* in non-neutropenic patients; 0.7–1 mg/kg/day for patients with neutropenia; and 1 mg/kg/day for infections caused by *Candida glabrata* and *Candida krusei* [11]. In the case of mucormycosis, the recommended dose is 1–1.5 mg/kg/day [1].

It has traditionally been recommended to start amphotericin B deoxycholate administration after a previous test dose of 1 mg, increasing the doses thereafter. This empirical recommendation delays the administration of the full dose of the drug, which is vital in these severe cases of IFI, and thus does not seem to be justified nowadays. In addition, initial administration of amphotericin B deoxycholate at a high dose (1 mg/kg/day by continuous infusion) without a previous test dose has been proved to be safe in a clinical study [10]. Amphotericin B deoxycholate is diluted in 500 mL of 5% dextrose through an independent central venous catheter, and is administered with 1000 mL of saline solution, and when possible, by 24-h continuous infusion. Treatment with amphotericin B deoxycholate requires monitoring of creatinine, sodium, potassium, bicarbonate and magnesium levels [8–10].

AMPHOTERICIN B LIPID FORMULATIONS

Three lipid formulations of amphotericin B deoxycholate are currently available: amphotericin B lipid complex, amphotericin B colloidal dispersion and liposomal amphotericin B. In comparison with amphotericin B deoxycholate, these compounds reach higher concentrations in the liver and spleen, and lower concentrations in the kidneys. Lipid formulations have the same mechanism of action and the same spectrum of activity as amphotericin B deoxycholate [12].

Lipid amphotericin B formulations, especially liposomal amphotericin B, are less nephrotoxic than amphotericin B deoxycholate [13–15]. Table 2 shows the renal toxicity associated with the different amphotericin B formulations. Infusion-related adverse effects are frequent with lipid amphotericins [13], amphotericin B colloidal dispersion being responsible even more frequently than amphotericin B deoxycholate, followed by amphotericin lipid complex and liposomal amphotericin B [16,17]. Cases of severe pulmonary reactions have been described during the administration of amphotericin B lipid complex, some of them leading to death [18]. With the first dose of liposomal amphotericin B, an acute reaction affects up to 35% of patients, with three possible presentations: (i) chest pain, dyspnoea and hypoxia; (ii) severe abdominal, flank or leg pain; or (iii) flushing and urticaria. These symptoms, which may be severe, are reversed with the suspension of the infusion and administration of diphenhydramine, and do not necessarily appear again with subsequent doses of liposomal amphotericin B [19].

Randomised studies comparing the efficacy of amphotericin B deoxycholate with that of the lipid formulations of amphotericin B are scarce. According to these few studies, amphotericin B colloidal dispersion is as efficacious as amphotericin B deoxycholate in the treatment of invasive aspergillosis [17] as well as in the empirical treatment of persistent neutropenic febrile patients [13]. This traditional indication for

Table 2. Nephrotoxicity of the different lipid formulations of amphotericin in clinical trials

	Nephrotoxicity[a] (%)	Reference
Amphotericin B deoxycholate infused over 24 h vs. 4 h	15 vs. 28	[8]
Amphotericin B colloidal dispersion vs. amphotericin B deoxycholate	20 vs. 52	[13]
Liposomal amphotericin B vs. amphotericin B deoxycholate	19 vs. 34	[15]
Liposomal amphotericin B vs. amphotericin B lipid complex	14 vs. 42	[17]

[a]Defined as two times baseline creatinine level during treatment.

antifungal therapy has recently been questioned, since empirical treatment seems to be neither more effective than placebo nor an improvement upon the results obtained with directed antifungal treatment [20].

Liposomal amphotericin B is more effective than amphotericin B deoxycholate in the treatment of severe histoplasmosis in AIDS patients [21], and is similarly effective in the empirical treatment of neutropenic patients with persistent fever [15]. Lipid formulations are considerably more expensive than conventional amphotericin B [12].

Lipid amphotericin B formulations are indicated for the treatment of those IFIs in which amphotericin B deoxycholate has failed or has caused adverse effects. In addition, liposomal amphotericin B has been approved for the treatment of neutropenic patients with persistent fever at a dose of 3 mg/kg/day [15]. Lipid formulations of amphotericin B require higher doses to achieve an efficacy equal to that of amphotericin B deoxycholate. In general, 5 mg/kg/day of lipid formulations is equivalent to 1 mg/kg/day of conventional amphotericin B. The recommended dose of liposomal amphotericin B in both adult and paediatric patients is 3–5 mg/kg/day, depending on the severity and cause of the infection. Liposomal amphotericin B is administered intravenously by continuous infusion for 30–60 min, diluted in 5% glucose solution, at a concentration of 0.20–2 mg/mL. Amphotericin B lipid complex is administered at a dose of 5 mg/kg/day by intravenous infusion, diluted in 5% glucose solution, at an infusion rate of 2.5 mg/kg/h. The manufacturer of this product recommends an initial test dose of 1 mg. The recommended dose of amphotericin B colloidal dispersion is 3–4 mg/kg/day [12].

FLUCYTOSINE

Flucytosine is a fluorinated cytosine analogue that acts by inhibiting DNA synthesis in the fungus. Its spectrum of activity is limited to *Candida* spp. and *Cryptococcus neoformans*. When combined with amphotericin B deoxycholate, it shows a synergistic or additive effect against both species. Primary resistance to flucytosine is rare, except for *Candida krusei*. Secondary resistance rapidly develops when flucytosine is used in monotherapy [1].

Flucytosine is considered to be an antifungal agent with a time-dependent activity and a short PAE [5]. Oral absorption of flucytosine is rapid and complete. It barely binds plasma proteins, and has good tissue penetration; its levels in cerebrospinal fluid (CSF) reach nearly 75% of those in plasma. Flucytosine's half-life is 4 h. It is eliminated in urine without previous metabolic change; dose adjustment is therefore needed in cases of renal impairment. Bone marrow suppression, nausea and vomiting and, especially, skin rash are the main adverse effects [1]. Cytosine arabinoside inhibits flucytosine, so their combined administration is contraindicated. Flucytosine is contraindicated during pregnancy. The main indication for flucytosine is the treatment of cryptococcal meningitis, in combination with amphotericin B deoxycholate. This combination is the treatment of choice because, when compared with amphotericin B deoxycholate in monotherapy, it takes much less time to achieve CSF sterilisation [22,23]. The recommended dose of flucytosine is 25–37 mg/kg/6 h administered orally. In cases of renal impairment, monitoring of flucytosine plasma levels is recommended, in order to maintain optimum levels (between 30 and 80 mg/L) [11]. When creatinine clearance is 26–50 mL/min, the total dose must be reduced to 75 mg/kg/day, and when creatinine clearance is 13–25 mL/min, to 37 mg/kg/day. In cases of endocarditis and meningitis caused by *Candida* spp., it is recommended to combine flucytosine with amphotericin B deoxycholate [1,11]. Flucytosine, when combined with fluconazole, is an alternative treatment for cryptococcal meningitis [23]. Flucytosine is available as 250-mg and 500-mg capsules, and as a solution, 2.5 g in 250 mL, for intravenous administration.

AZOLES

Azoles constitute a family of systemic antifungal agents that are classified according to the number of nitrogen atoms in their ring structure, either as imidazoles (miconazole and ketoconazole), with two nitrogen molecules, or as triazoles (itraconazole, fluconazole and voriconazole), with three molecules. Imidazoles have been displaced by triazoles in the treatment of IFI [1].

Azoles inhibit lanosterol-14α-demethylase, thus interrupting the conversion of lanosterol to ergosterol. Depletion of ergosterol, a major component

of the fungal cell membrane, alters its permeability and causes either death of the fungus or inhibition of growth [2].

The spectrum of activity of fluconazole includes *Candida* spp. (except for *Candida krusei*), *Cryptococcus neoformans*, *Trichosporon* spp., *H. capsulatum*, *Coccidioides immitis*, *B. dermatitidis*, *Paracoccidioides brasilensis* and *Sporothrix schenckii*. Itraconazole is also active against *Aspergillus* spp., and voriconazole extends its activity, in a variable fashion, to *Fusarium* spp. and *Scedosporium apiospermum*. Azoles are not active against zygomycetes and *Scedosporium prolificans*.

Primary resistance to azoles is well-known, *Candida krusei* and fluconazole being the best example of this [2]. Secondary resistance during treatment is well-documented in *Candida* strains causing stomatitis and oesophagitis in AIDS patients and in HSCT patients [24,25]. Cross-resistance with other azoles is not universal, but in general those strains resistant to fluconazole have higher MICs of other azoles as well. Increased use of azoles, especially fluconazole, is associated with an increase in less susceptible *Candida* species, such as *Candida glabrata* and *Candida krusei*. Similarly, the occurrence of infections caused by zygomycetes has been related to the introduction of voriconazole for treatment and prophylaxis in HSCT recipients [26,27].

Standardisation of azole susceptibility testing has allowed, for the first time in the context of antifungal treatment, the establishment of clinically useful cut-off points, as suggested by recent data in patients with candidaemia in whom a close correlation among dosage, the MIC of fluconazole and response to therapy has been demonstrated [28].

Triazoles are fungistatic agents that are active against *Candida* spp., their activity being time-dependent and showing a prolonged PAE [5]. These drugs require initial loading doses in order to rapidly reach a steady state. Triazoles inhibit the cytochrome P450 enzyme system, thus causing numerous pharmacological interactions of variable intensity, depending on the compound used (Table 3). Triazoles are contraindicated during pregnancy, and their use is not recommended during breast-feeding. Unlike other antifungal agents, triazoles are available for both oral and intravenous administration, and are therefore the drugs of choice in the sequential treatment of IFI.

Fluconazole

Fluconazole exhibits excellent oral absorption (90%), influenced by neither oral intake nor gastric pH. Protein binding is very minimal, unlike with other triazoles. In CSF, fluconazole levels reach nearly 70% of those in plasma. It is mainly eliminated without metabolic change through glomerular filtration, and thus reaches high renal levels. It requires a 50% reduction in dose whenever creatinine clearance is below 50 mL/min, and a 25% reduction if creatinine clearance is *c.* 20 mL/min. In haemodialysis patients, an entire dose of fluconazole must be administered after each haemodialysis session [29]. Its half-life is 30 h, but in neonates the half-life is longer, so in the first 2 weeks of life the interval between doses is 72 h, and in the third and fourth weeks it is 48 h.

Fluconazole is the safest and best tolerated triazole. Its administration is interrupted by adverse events in only 1.5% of patients. Nausea, vomiting, skin rash and transient increases in the plasma levels of transaminases are the most common adverse effects [29].

Fluconazole inhibits cytochrome P450, CYP3A4 and CYP2C9 isoenzymes. The pharmacological interactions of fluconazole are described in Table 3. Simultaneous administration of astemizole, terfenadine and cysapride with fluconazole is contraindicated [29].

Fluconazole is indicated for front-line treatment of invasive candidiasis in patients not previously treated with azoles as well as for the sequential treatment of both this IFI [11] and cryptococcal meningitis [22,23]. Fluconazole is the treatment of choice for meningitis caused by *Coccidioides immitis*. In primary prophylaxis, fluconazole is effective in the prevention of invasive candidiasis in allogeneic HSCT recipients [30], cryptococcosis in AIDS [31] patients and IFI in infants with birth weights of less than 1000 g [32]. In secondary prophylaxis, fluconazole is efficient in the prevention of relapsing cryptococcal meningitis and coccidiomycosis in HIV-infected patients [31].

Itraconazole

Itraconazole is available as capsules, as oral solution and, recently, in solution for intravenous administration. These last two formulations have cyclodextrin as an excipient, which facilitates

Table 3. Drug interactions with azoles

Drugs	Type of interaction	Fluconazole	Itraconazole	Voriconazole
Rifampin	Decrease	Caution	Not recommended	Contraindicated
Phenobarbital	azole levels		Caution	Contraindicated
Carbamazepine			Caution	Contraindicated
Nevirapine		Caution	Not recommended	Caution
Astemizol, terfenadine, cisapride, pimozide, quinidina	Increase drug levels	Contraindicated	Contraindicated	Contraindicated
Disopyramide			Caution	
Dofetilide, mizolastide levomethadyl			Contraindicated	
Sirolimus			Caution	Contraindicated
Cyclosporin		Caution	Caution	Dose should be halved
Tacrolimus		Caution	Caution	Dose should be reduced to a third
Ergot alkaloids			Caution	Contraindicated
Oral anticoagulants		Caution	Caution	Caution
Sulfonylureas		Caution		Caution
Simvastatina, lovastatina, atorvastatina		Caution	Contraindicated	Caution
Midazolam oral, triazolam		Caution	Contraindicated	Caution
Vinca alkaloids			Caution	Caution
Trimetrexate, docetaxel, busulfan, cilostazol, eletriptan			Caution	
Halofantrine			Caution	
Alfentanil		Caution	Caution	
Omeprazole				Dose should be halved
Zidovudine		Caution		
Calcium channel blockers			Caution	
Phenytoin	Two-way	Caution	Caution	Not recommended
Rifabutim	interactions	Caution	Not recommended	Not recommended
Ritonavir		Caution	Caution	Contraindicated[a]
Efavirenz			Caution	Contraindicated

Contraindicated: concomitant administration is contraindicated.
Caution: special precautions and monitoring of patient and drug levels are required.
[a]Voriconazole co-administered with 400 mg twice-daily of ritonavir is contraindicated. There are no data on the interaction when boosting doses of ritonavir (RTV) (100–400 mg/day) are given with voriconazole.

itraconazole solubility. The oral absorption of itraconazole capsules is irregular, and increases with gastric pH, food and cola drinks. The oral solution is better absorbed than are capsules; absorption increases with fasting and does not change with gastric pH variations. Itraconazole circulates strongly bound to plasma proteins and barely penetrates the CSF. It is metabolised in the liver and eliminated in bile and urine. Cyclodextrin is eliminated without metabolic change through glomerular filtration. In patients with hepatic dysfunction, a reduction in the dose of itraconazole is required. In patients with creatinine clearance below 30 mL/min, both oral and intravenous solutions of itraconazole are contraindicated [33]. Cyclodextrin, the excipient used for itraconazole and voriconazole formulations, produces pancreas adenocarcinoma in rats. The clinical relevance of this carcinogenic effect is unknown [34].

Itraconazole's adverse effects are rare and, in general, mild. Nausea, vomiting, diarrhoea and

asymptomatic transaminase elevations are the main adverse effects. Intolerance to itraconazole is more frequently observed with the oral solution. Isolated cases of severe hepatotoxicity, with hepatic failure and death, have also been described. Intravenous itraconazole exhibits a negative inotropic effect and therefore its use should be avoided in patients with cardiac dysfunction [34].

Itraconazole interactions are more frequent and significant than those of fluconazole, as shown in Table 3. Simultaneous administration of itraconazole and astemizole, terfenadine, cisapride, lovastatin, simvastatin, atorvastatin, quinidine, oral midazolam, rifampin, rifabutin, phenytoin and ergotamine alkaloids is contraindicated. Monitoring of itraconazole plasma levels is recommended when administering capsules or oral solution, in order to achieve concentrations above 0.5 mg/L, which seem to provide protection against IFI. With the oral solution, levels ≥0.5 mg/L are reached in 90% of patients receiving itraconazole [35]. The efficacy and safety of itraconazole in children have not been assessed, so its use is not recommended in this patient population [34].

Itraconazole, in oral and intravenous solution, is indicated for the empirical antifungal treatment of persistent febrile neutropenia, since its efficacy is similar to that of amphotericin B deoxycholate and it is better tolerated [36]. Itraconazole is the treatment of choice in sporotrichosis and endemic mycoses with no meningeal involvement in immunocompetent patients. It has also been approved as an alternative treatment for invasive aspergillosis, based on non-comparative open studies [37,38]. Itraconazole solution, in both oral and intravenous formulations, is as effective as fluconazole in the prophylaxis of IFI in haematological patients with neutropenia and in HSCT recipients [35,39]. Continuous prophylaxis with itraconazole reduces the incidence of IFI in children with chronic granulomatous disease [40]. In AIDS patients, itraconazole is recommended for primary and secondary prophylaxis of histoplasmosis, and it is also very effective in the prevention of relapsing infection caused by *Penicillium marneffei* [41].

The recommended dose of itraconazole by injection is 200 mg twice-daily for the first four doses, followed by 200 mg once-daily for up to 14 days. Each intravenous dose should be infused over 1 h. Afterwards, treatment should be continued with itraconazole oral solution or capsules 200 mg twice-daily [34].

Voriconazole

Voriconazole is the first of a new generation of triazoles, available in capsules and cyclodextrin solution for intravenous administration. Its oral bioavailability is high, being maximum when administered during fasting (before meals or food intake). Its half-life is 6–12 h, and 58% of the drug is usually bound to plasma proteins. It reaches very high levels in the CSF. Voriconazole is metabolised in the liver by the CYP450 enzyme system, especially the CYP2C19, CYP2C9 and CYP3A4 isoenzymes. In patients with moderate renal failure (creatinine clearance <50 mL/min), intravenous administration should be avoided. In patients with Child's A and B grades of liver dysfunction, the recommended voriconazole maintenance dose should be reduced, in light of the low weight (under 40 kg) of the patients. Treatment with voriconazole is not recommended in patients with Child's C grade of cirrhosis [42]. Voriconazole is well-tolerated generally, its most common adverse effects being transient visual alterations, with blurred vision, colour change, photosensitivity and/or photophobia. Other adverse effects include nausea, headache, skin rash and reversible transaminase elevations. Uncommon cases of serious hepatic reactions, including fulminant hepatic failure, have also been described [42].

Since voriconazole is metabolised by the CYP3A4 pathway, it has many and very relevant drug interactions (Table 3). Some of them are with astemizole, terfenadine, cisapride, pimozide or quinidine with voriconazole when simultaneously administered, and these are contraindicated due to the risk of prolonged QTc, and the risk of *torsade de pointes* increases with such combinations. It is also contraindicated in combination with rifampin, phenobarbital and carbamazepine, since these drugs lead to a rapid and profound drop in voriconazole plasma levels; and it is contraindicated in combination with sirolimus, due to the increased levels of this immunosuppressant when given simultaneously with voriconazole, and with ergotaminic alkaloids, because of the risk of ergotism. It is also recommended to avoid the concomitant use of voriconazole with rifabutin and phenytoin [42].

Voriconazole is the treatment of choice for invasive aspergillosis. In a randomised open study, it demonstrated a higher efficacy than amphotericin B deoxycholate, improving the survival rate [43]. Voriconazole is effective as salvage therapy in cases of invasive candidiasis and cryptococcosis and as front-line treatment for *Fusarium* spp. and *Scedosporium apiospermum* infections [44]. Voriconazole was not approved for the empirical management of persistent febrile neutropenia, since it did not meet the discussed criteria of equivalence with liposomal amphotericin B [45].

The recommended dose of intravenous voriconazole is 6 mg/kg/12 h on the first day of treatment, followed by 4 mg/kg/12 h thereafter. In patients weighing <40 kg, these doses must be reduced to 200 mg/12 h and 100 mg/12 h, respectively. Voriconazole is not recommended for children less than 2 years of age [42].

CASPOFUNGIN

Caspofungin belongs to a new class of antifungal drugs, the echinocandins, which act by non-competitively inhibiting the synthesis of 1,3-β-glucan, an essential component of the cell walls in many yeasts and moulds, which is not present in the cell walls of mammals. Caspofungin has fungicidal activity against all *Candida* species as well as potent inhibitory activity *in vitro* against *Aspergillus* spp. It is not active against *Cryptococcus neoformans*, *Trichosporon* spp., *Scedosporium prolificans*, *Rhizopus* spp. and *Fusarium* spp. [46].

Caspofungin activity against *Candida* spp. is fungicidal and concentration-dependent, and has a prolonged PAE [5]. It is available for intravenous use only, and more than 90% of the drug circulates bound to plasma proteins. In liver, kidneys, spleen and lungs, it reaches concentrations higher than those in plasma. It is metabolised in the liver, independently of the CYP450 system. A reduction of the caspofungin maintenance dose to 35 mg daily is recommended in cases of moderate hepatic dysfunction, and interruption of the drug is recommended in cases of severe hepatic failure. Caspofungin does not require dose adjustment for renal failure or in haemodialysis patients. Its prolonged half-life, 9–11 h, allows administration of a single daily dose [46].

Caspofungin is safe and well-tolerated. Its main adverse effects are fever, phlebitis, headache and reversible moderate elevation of transaminases. Simultaneous administration with efavirenz, carbamazepine, phenytoin, phenobarbital or dexamethasone can reduce caspofungin efficacy; therefore, increasing the dose to 70 mg daily is recommended when it is given concomitantly with any of these drugs. Cyclosporin increases the caspofungin AUC in 35% of cases and causes a transient elevation of transaminases, so concomitant use of the two drugs should be limited to those patients in whom the benefits are expected to outweigh the potential risks [46]. In recent studies, the simultaneous administration of caspofungin and cyclosporin was not associated with an increased risk of relevant hepatic toxicity [47,48].

Caspofungin is indicated for the treatment of invasive candidiasis in adult patients, based on a randomised study in which caspofungin was demonstrated to be as effective as amphotericin B deoxycholate, but with less toxicity [49]. It is indicated for the management of invasive aspergillosis in adult patients following clinical failure or intolerance to amphotericin B deoxycholate, lipid formulations of amphotericin B and/or itraconazole, according to the data from a non-comparative open study [50]. Finally, caspofungin has been approved for the empirical treatment of patients with persistent febrile neutropenia, since it is as effective as, and better tolerated than, liposomal amphotericin B [51].

A single 70-mg loading dose should be administered on day 1, followed by 50 mg daily thereafter. In patients weighing more than 80 kg, after the initial 70-mg loading dose, 70 mg daily is recommended. Caspofungin has not been studied in paediatric patients, so its use in patients under 18 years of age is not recommended [46].

Table 4 shows dosages and methods of administration for all antifungal agents in the treatment of adults and special populations.

COMBINATION ANTIFUNGAL THERAPY

Combination therapy has shown superior results to monotherapy in several bacterial and viral infections; it has thus been proposed for the treatment of IFIs, especially aspergillosis. The clinical rationale for combination antifungal therapy is limited to the results of only three

Table 4. Antifungal drug dosage and administration in special populations

Antifungal drugs	Loading dose	Adult dosage	Infusion rate	Food effect	Adjustment for renal failure	Adjustment for hepatic failure	Use in paediatric patients	Pregnancy
AB deoxycholate	No	0.6–1.5 mg/kg/day	6–24 h	–	No	No	Yes	Should be used
AB lipid complex	No	5 mg/kg/day	2 h	–	No	No	Yes	Not recommended
AB colloidal dispersion	No	3–4 mg/kg/day	3–4 h	–	No	No	Yes	Not recommended
Liposomal AB	No	3–5 mg/kg/day	0.5–1 h	–	No	No	Yes	Not recommended
Flucytosine (intravenous)	No	25 mg/kg/6 h	0.5 h	–	Yes	No	Yes	Contraindicated
Flucytosine (oral)	No	25 mg/kg/6 h	–	No effect	Yes	No	Yes	Contraindicated
Fluconazole (intravenous)	6–12 mg/kg × 2	6 mg/kg/day	0.5 h	–	Yes	No	Yes	Contraindicated
Fluconazole (oral)	No	400 mg/day	–	No effect	Yes	No	Yes	Contraindicated
Itraconazole (intravenous)	200 mg/12 h ×4	200 mg/day	1 h	–	Yes	Yes	No	Contraindicated
Itraconazole (oral solution)	No	200 mg/12 h	–	Without food	Yes	Yes	No	Contraindicated
Itraconazole (oral capsules)	No	200 mg/12 h	–	With food	Yes	Yes	No	Contraindicated
Voriconazole (intravenous)	6 mg/kg/12 h × 2	4 mg/kg/12 h	1–2 h	–	Yes	Yes	Yes (>2 years)	Contraindicated
Voriconazole (oral)	400 mg/kg/12 h × 2	200 mg/12 h	–	Without food	Yes	Yes	Yes (>2 years)	Contraindicated
Caspofungin (intravenous)	70 mg/day × 1	50 mg/day	1 h	–	No	Yes	No	Not recommended

AB, amphotericin B.

prospective randomised studies. The first study, carried out in patients with cryptococcal meningitis, demonstrated that the combination of amphotericin B deoxycholate (0.3 mg/kg/day) and flucytosine (150 mg/kg/day) was more effective than amphotericin B deoxycholate as monotherapy, with a higher incidence of response, fewer relapses and more rapid CSF sterilisation [52]. The second study, performed in HIV-infected patients with cryptococcal meningitis, demonstrated that with the combination of amphotericin B deoxycholate (0.7 mg/kg/day) and flucytosine (100 mg/kg/day), it takes less time to sterilise CSF than with amphotericin B deoxycholate as monotherapy [22]. Mortality rates were the same in both groups. The third study demonstrated that the combination of amphotericin B deoxycholate (0.7 mg/kg/day) with fluconazole (800 mg/day) improves the rates of clinical and microbiological response in non-neutropenic patients with candidaemia when compared with fluconazole as monotherapy, although it did not decrease the rate of mortality [53].

Concerning invasive aspergillosis, no randomised prospective studies assessing combination antifungal therapy are available. In an observational study performed in patients with invasive aspergillosis in whom amphotericin B deoxycholate had failed, treatment with caspofungin plus voriconazole reduced mortality when compared with an historical control group treated with voriconazole alone [54]. However, reliance upon these results is limited by several factors inherent to the study: it was not a randomised study, the comparison was made with an historical control group, and the current standard treatment for aspergillosis was not amphotericin B deoxycholate, but voriconazole [43].

In conclusion, combination antifungal therapy is more effective than monotherapy in the management of cryptococcal meningitis and candidaemia, but has not been assessed yet in invasive aspergillosis. Combinations of echinocandins with azoles or amphotericin B deserve further well-designed studies in order to answer the key question: is combination therapy superior to monotherapy in treating invasive aspergillosis? In the meantime, we can only affirm that combination therapy for invasive aspergillosis is more expensive and carries a higher risk of toxicity and adverse drug interactions than monotherapy.

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