

Chapter 2

Antifungal Drugs

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Abstract Fungal infections have increased globally due to the increment of the size of population at risk for fungal infection, which is a consequence of the increased use of immunosuppressive drugs and invasive techniques for advanced life support and extended life expectancy among other reasons. Although invasive fungal infections currently are a significant cause of mortality among critically ill patients, development and approval of new systemic antifungal drugs have not occurred at the same rate as the increase in the number of fungal infections. Only one new class of systemic antifungal drugs, Echinocandins, has been included in the antifungal armamentarium in the last 20 years.

The purpose of this chapter is to review the systemic antifungal drugs currently in use, including new insights on pharmacologic and pharmacokinetics properties, clinical indications, adverse events, and resistance mechanisms. Resistance to antifungal drugs is particularly important because it has increased for every drug, including the echinocandins class. New formulations of triazol drugs and combination therapy is also highlighted.

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2.1 Polyenes (Amphotericin B Deoxycholate and Its Lipid-Associated Formulations)

2.1.1 Amphotericin B Deoxycholate

Amphotericin B (Amph B), derives from *Streptomyces nodosus*, belongs to a group of polyene macrolides characterized by a macrocyclic ring of lactone. Due to its low water solubility, oral bioavailability is low. This drug can be administered intravenous, intrathecal, intraarticular, intravesical, and in surgical sites. This is one of the oldest antifungal drugs but is still used in the fungal therapy because of its broad activity spectrum.

Although amph B is fungicidal in vitro, it may be fungicidal or fungistatic in vivo depending on the concentration of the drug achieved in body fluids and the susceptibility of the fungus [1].

2.1.1.1 Chemical Structure

Amph B is a heptaene macrolide compound comprising of seven conjugated double bonds within the main ring. This drug has an amino sugar called mycosamine, which in the pyranose form is linked to the hydroxyl group at C-19 of the macrolactone ring of amph B through a glycoside side chain, and a free carboxyl group on the macrocycle. Amph B has a molecular formula of $C_{47}H_{73}NO_{17}$ and a molecular weight of 924.09 [2, 3] (Fig. 2.1).

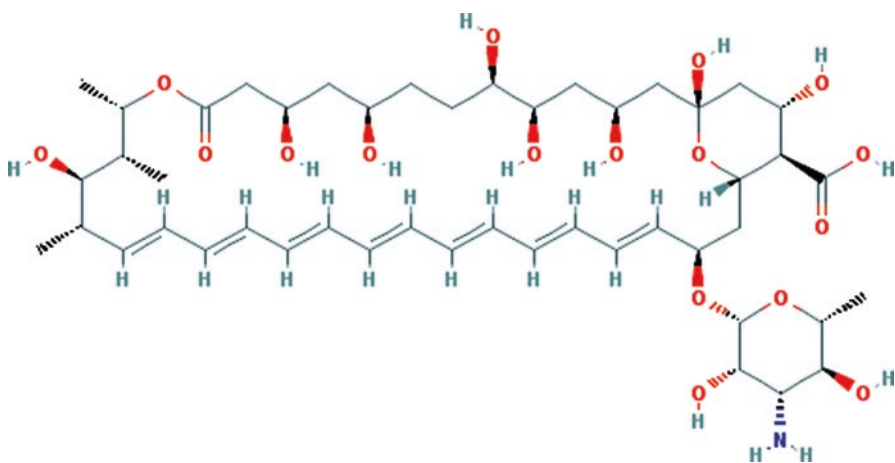


Fig. 2.1 Chemical structure of Amphotericin B deoxycholate. Source: Reference [4]

2.1.1.2 Mechanism of Action

Amph B exerts its antifungal action by binding to ergosterol in the fungal cytoplasmic membrane resulting in the formation of pores that causes an increase in their permeability with leakage of small molecules from the cytoplasm, leading to fungal death. This drug may have other effects as an oxidative damage to fungal cell or by immunomodulatory properties on the host cells [5–7].

2.1.1.3 Pharmacokinetics and Pharmacodynamics

Amph B is not appreciably absorbed when taken orally or subsequent to aerosol administration. Then, the intravenous formulation should be used for fungal systemic diseases. After IV administration, this drug is highly bound (>90%) to plasma proteins mainly to albumin, is weakly dialyzable and it is taken up by reticulo-endothelial organs, especially the liver, spleen and lung [8–10].

The activity of amph B depends on its concentration and prolonged post-antifungal effect [11]. Its elimination is biphasic. Initially, it is quickly removed with a half-life of about 24 h, while the second elimination phase has a half-life of up to 15 days [12]. In vitro evaluations have shown evident concentration-dependent killing and maximal antifungal activity at concentrations exceeding the MIC by two- to tenfold [11, 13]. In vivo time-kill studies with amph B against different *Candida* species have also shown an improved rate and extent of killing with increasing drug concentrations [14, 15].

Additionally, an in vivo study using a rabbit model of invasive pulmonary aspergillosis to evaluate the pharmacokinetics and pharmacodynamics of amph B deoxycholate, amph B lipid complex (ABLC) and liposomal amph B (L-AmB) found that all formulations of amph B induced a dose-dependent reduction in markers of lung injury and circulating fungus-related biomarkers. Dosing of L-AmB of 3 mg/kg/day predicts complete suppression of galactomannan and (1, 3)-D-glucan levels in the majority of patients [16].

The amph B concentration in urine is low, finding only 3% of the dose, and its penetration in cerebrospinal fluid is limited (2–4% of serum concentrations) [17]. Amph B goes through minimally into the vitreous humor and normal amniotic fluid. In the peritoneal fluid, pleura, or joint, fewer than 50% of the serum levels are obtained [18]. Serum level of the drug is not influenced by hepatic or renal function, or by hemodialysis or peritoneal dialysis. Even in anuric and nephrectomized patients, the drug serum levels and its elimination are just the same as in healthy patients. It seems that amph B is eliminated principally by metabolic conversion or by the bile [9, 19]. However, the metabolites are not yet well known.

2.1.1.4 Spectrum of Activities and Resistance

Amph B has activity against a wide range of fungi including most yeasts, and hyaline and dematiaceous molds. Among the yeast, *Candida* isolates resistant to polyenes are still infrequent. *C. lusitanae* and *Trichosporum beigelii* are two fungi that

have intrinsic resistance, and recently some *C. krusei* and *C. glabrata* strains with high MICs to amph B has been reported [20–22]. In the group of molds, *Aspergillus terreus*, *Scedosporium apiospermum*, *Scedosporium prolificans*, and *Fusarium* species are usually resistant to amph B [23].

Although breakpoints for polyenes are not available, most microbiologist use a MIC of ≥ 1 $\mu\text{g/mL}$ to determine if an isolate is not susceptible to amph B. Reduction or absence of ergosterol in the fungal cell membrane has been associated with resistance. These alterations could be due to mutations in genes coding some of the enzymes involved in the synthesis of ergosterol. The mechanisms involved in the resistance of *C. albicans* isolates to the amph B include a double loss in function of both ERG3 (C-5 sterol desaturase) and ERG11 (lanosterol 14 α demethylase) [24, 25]. It has also been identified isolates amph B resistant lacking ERG2, encoding C-8 sterol isomerase, and ERG6, encoding C-24 sterol methyltransferase [26–28].

2.1.1.5 Clinical Uses

Despite the emergence of new antifungal drugs in the last decades, amph B deoxycholate or its lipid formulations are still recommended as primary treatment for several severe or refractory fungal infections or as alternative therapy for other forms of these diseases. According to the Infectious Diseases Society of America (IDSA) guidelines for the management of candidiasis [29], amph B deoxycholate is recommended for the treatment of neonates with disseminated candidiasis or candidiasis in central nervous system, for patients with asymptomatic candiduria who undergo urologic procedures, and for symptomatic candida cystitis or symptomatic ascending candida pyelonephritis due to fluconazole-resistant *C. glabrata* or to *C. krusei*. This drug is recommended as alternative in the treatment for fluconazole-refractory oropharyngeal/esophageal candidiasis. Amph B deoxycholate or lipid formulations are also indicated for the treatment of cryptococcal meningitis, mucormycosis, moderately severe to severe forms of blastomycosis and histoplasmosis [30–33].

Aerosolized amph B, in their different formulations, is utilized as prophylaxis (either alone or in combination with systemic antifungals) in patients at highest risk of invasive fungal infections. A recent meta-analysis presented evidence supporting the concept that the prophylactic use of aerosolized amph B effectively reduces the incidence of invasive pulmonary aspergillosis among high-risk patients [34]. The current IDSA guidelines for the diagnosis and management of aspergillosis stated that aerosolized formulations of amph B may be considered for prophylaxis in patients with prolonged neutropenia and in lung transplant recipients (weak strength recommendation; low-quality evidence) [35].

Because of the low intraocular levels attained with systemic administration, intravitreal injection of amph B is useful to reach high confined antifungal activity for the treatment of severe macular involvement and vitritis. The IDSA guidelines suggest treatment with systemic antifungal drug plus local amph B deoxycholate, 5–10 $\mu\text{g}/0.1$ mL sterile water, for *Candida* chorioretinitis without vitritis and with

macular involvement, and for *Candida* chorioretinitis with vitritis [29]. In addition, IDSA guidelines recommend intraocular amphotericin B with partial vitrectomy as primary treatment of *Aspergillus* endophthalmitis and keratitis [34]. There are controversial reports on toxicity of intravitreal injection of amphotericin B deoxycholate in humans, some of them have described low toxicity and others have reported toxic uveitis [36–41].

There is not a good evidence to recommend bladder irrigation with amphotericin B deoxycholate for treatment of cystitis but, when this infection is due to fluconazole-resistant species, such as *C. glabrata* and *C. krusei*, this method of delivering the antifungal drug directly to the affected site could be used [29, 42].

2.1.1.6 Dosing

Dosing of amphotericin B deoxycholate in adults with normal renal and hepatic function is 0.5–1 mg/kg daily for candidemia, other invasive candidiasis and for endemic dimorphic fungal infections; 1–1.5 mg/kg daily for invasive aspergillosis; 0.3 mg/kg daily for esophageal and oropharyngeal candidiasis; 0.7 mg/kg daily for empiric treatment of febrile neutropenia; and 0.7–1 mg/kg daily (usually with 5-flucytosine) for cryptococcal meningitis in the induction phase of the therapy.

2.1.1.7 Adverse Events and Toxicity

Acute toxicity related to amphotericin B administration is due to stimulation by the antifungal drug of inflammatory cytokine production from innate immune cells via an interaction that requires CD14 and Toll-like receptors [43]. The most frequent acute effects are nausea, vomiting, rigors, fever, hypertension/hypotension, and hypoxia. Other acute adverse events with rare presentation are ventricular arrhythmias, bradycardia, and severe hypertension [44–46]. In addition, two cases with fatal leukoencephalopathy associated with the intravenous administration of the amphotericin B has been reported [47].

Chronic toxicity is referred commonly to nephrotoxicity, but there are other events such as hypomagnesemia, hypokalemia, hyperphosphatemia, anemia, and rare cases of hyperbilirubinemia [48–51]. Reports of anemia of any degree of severity ranges from 33 to 63% in different studies [52–54].

The incidence of nephrotoxicity due to amphotericin B is high, ranging from 49 to 65% [55, 56]. This toxicity is result of renal vasoconstriction producing reduction in glomerular filtration rate, and of direct effect on tubular epithelial cell membranes forming pores. The modification in the permeability of the tubular cell membrane will allow the back diffusion of hydrogen ions thereby weakening the acid elimination [57]. There are some factors that influence the nephrotoxicity of amphotericin B such as cumulative dose, average daily dose, abnormal baseline renal function, concomitant nephrotoxic drugs, and patient's risk category (bone marrow transplant, solid organ transplantation) [58]. Nephrotoxicity is cumulative and dose dependent but it is

reversible after amph B treatment is stopped [58, 59]. This toxicity can be decreased by hydration and electrolyte supplementation before amph B infusion [60–63]. In the case of aerosolized amph B, the most common side effects are cough, bad taste, nausea and vomiting; most of them mild or moderate severity [64–67].

2.1.1.8 Contraindication

Amph B is contraindicated in those patients who have known hypersensitivity to this anti-fungal drug, and because the increment risk of nephrotoxicity and hearing impairment, its use is contraindicated with the simultaneous administration of the following drugs: amikacin, cidofovir, cyclosporine, ioversol, neomycin, streptozocin, and tacrolimus. Amph B should be discontinued before iodinated contrast media administration [68].

2.1.1.9 Drug Interactions

Corticosteroids, thiazide, loop diuretics, and neuromuscular blockers increase risk of amph B-induced hypokalaemia. Amph B can also increase the risk of digoxin toxicity [69]. Use of alternative drugs or monitoring of amph B associated adverse events is indicated when some of the above drugs needs to be used. Administration of amph B with most of the antiretrovirals does not cause interactions, but concomitant or sequential use with tenofovir increases the risk of nephrotoxicity [70]. In the same way, concomitant use of zidovudine and amph B results in increased risk of anemia and neutropenia [71].

2.1.1.10 Use in Special Population

Amph B and their lipid formulations do not need dose adjustment for patients with decreased renal function or in patients receiving hemodialysis or continuous renal replacement therapy or for those with moderate or severe hepatic disease.

Children In pediatric population, pharmacokinetic (PK)/pharmacodynamic (PD) indices of amph B are not validated; therefore, optimal dosing of this drug has not been defined. Amph B pharmacokinetic is very variable in neonates, which may lead to treatment failure or toxicity, and the lack of maturity of the blood-brain barrier in premature infants can be the basis of a better penetration of the antifungal to the CSF [72]. Compared with adults, amph B has a lower volume of distribution and faster clearance in children [72–76]. Even though most of PK studies in children encourage a dosage of 0.5–1 mg/kg/day, a population PK analysis suggested that younger children receiving 1 mg/kg/day might be underexposed, while older children may be overdosed at the same dose [75]. Another study showed that amph B doses of 0.25–1 mg/kg daily to infants causes lower serum concentrations compared with older children and adults [73, 76].

The preferred amph B deoxycholate pediatric dosing is 1–1.5 mg/kg/day. The infusion adverse events and nephrotoxicity due to amph B in children are similar to adults, but fever has been rarely described in infants [77, 78]. Children usually can tolerate higher doses than adults [79].

Pregnancy and Lactation Amph B is considered as category B (B: animal studies no risk, but human studies not adequate, or animal toxicity but human studies no risk) by the US FDA [80]. ABLC has been evaluated in animals without having found harms to the fetus [81]. Although, there are not well-conducted evaluations of amph B use in pregnancy, its use in pregnant women has been described repeatedly without confirmation of teratogenesis in their neonates [82–96].

This is the only systemic antifungal drug that is safe to use during the pregnancy and lactation period, although there are not published data in the last condition. Due to the properties of amph B such as its large molecular size, poor absorption, and high protein binding ability, breast milk amounts are probable insignificant [97]. There is limited information on the use of ABLC and L-AmB in pregnancy [98, 99].

It is known that amph B crosses the placenta and reaches fetal tissues where can persist some weeks after the mother has stopped the drug or given birth. This characteristic possibly would be due to placental deposit or deferred removal by the fetal kidneys [100].

2.1.2 *Lipid Formulations of Amphotericin B*

Lipid formulations of amph B have higher hydrophobicity, lower nephrotoxicity, and are distributed more efficiently to the sites of fungal infection or inflammation than amph B deoxycholate. The two lipid formulations available in most countries are liposomal amphotericin B (L-AmB) and amphotericin B lipid complex (ABLC), commercially available under the name AmBisome® (Gilead Sciences Inc., Foster City, CA, USA) and Abelcet (Enzon Pharmaceuticals Inc., Bridgewater, NJ, USA; Sigma Tau, Gaithersburg, MD; and Cephalon Limited, Welwyn Garden City, UK) respectively. A third lipid formulation, amphotericin B colloidal dispersion (ABCD), is no longer commercially available.

The lipid compositions and particle size are different between the amph B lipid formulations, producing distinct pharmacokinetic parameters and tissue distribution. Then, the lipid formulations of amph B cannot be used interchangeably to treat patients [101–103].

ABLC consists of amph B complexed to two phospholipids (1- α -dimyristoylphosphatidylcholine and 1- α -dimyristoylphosphatidylglycerol in a 7:3 molar ratio) in a 1:1 drug-to-lipid molar ratio to form a ribbon-like structure with a diameter of 1600–11,000 nm, making it the largest of the lipid formulations [104]. ABLC is taken by macrophages and becomes sequestered in the liver and spleen. It has lower circulating amph B serum concentrations, when it is compared with the amph B deoxycholate, but larger volume of distribution and clearance. Lung concentration of ABLC is higher than the obtained with L-AmB or amph B deoxycholate.

By contrast, molecules of L-AmB are smaller and not captured by the mononuclear phagocyte system. L-AmB consists of amphotericin B integrated into the lipid bilayer of small unilamellar liposomes, which are composed of hydrogenated soy phosphatidylcholine, cholesterol and distearoyl phosphatidylglycerol [105]. After a dose of L-AmB, it reaches a higher peak plasma level (C_{max}) than amphotericin B deoxycholate and a larger area under the concentration–time curve. The highest amphotericin B concentrations with the L-AmB administration are found in the liver and in the spleen, followed by kidneys and lungs. Levels in myocardium and brain tissues are low [106].

The ABLC mechanism of action requires that the fungal lipase, a heat labile extracellular product, produces a lipid breakdown within the ribbon-like material with subsequent discharge of amphotericin B into the tissues [107]. The suggested mechanism of action of L-AmB states it binds to the fungal cell wall and disintegrates itself, discharging amphotericin B that binds to ergosterol in the fungal cell membrane [108, 109]. Table 2.1 summarizes the characteristics of the different amphotericin B formulations.

Dissimilar results have been reported in relation to in vitro susceptibility of amphotericin B deoxycholate and lipid formulations. Montagna et al. found great correlation between the in vitro activities of amphotericin B deoxycholate and L-AmB against 604 clinical yeast isolates [125], while Johnson et al. found that MIC₅₀ and MIC₉₀ of ABLC were the same to or lower than those of amphotericin B deoxycholate when they were tested against 190 isolates from different fungal species, including *Aspergillus fumigatus*, *Candida* spp., and *Cryptococcus neoformans* [126]. In the later study, the L-AmB was the least active of the different amphotericin B preparations tested, showing 2–4 dilutions higher in their MICs than those of amphotericin B deoxycholate. Carrillo-Muñoz, studying the in-vitro susceptibilities of 120 clinical isolates of yeasts (including different species of *Candida*, *Rhodotorula rubra*, *Trichosporon* spp., *Cryptococcus laurentii* and *C. neoformans*), found no statistical significance among MICs of amphotericin B deoxycholate, ABLC, L-AmB and other antifungal drugs when evaluating all strains. However, there were differences in the activity of these drugs for individual species. Amphotericin B deoxycholate and ABLC had high MIC values for an isolate of *C. laurentii*, while L-AmB, had moderately low MIC for the same isolate. ABLC and L-AmB had higher mean MICs against *Trichosporon* spp., and L-AmB had high MIC₉₀ values for *C. glabrata* than amphotericin B deoxycholate [127].

In addition, the manufacturer of AmBisome® (L-AmB) claims that it has in vitro activity equivalent to amphotericin B deoxycholate against the following fungi: *Aspergillus* species, *Candida* species, *C. neoformans*, *Fusarium* species and *Blastomyces dermatitidis* [69].

Experimental studies carried out in animals demonstrated that it is necessary higher doses of the two lipid formulations to achieve the same or greater antifungal effect than the obtained by the amphotericin B deoxycholate [123, 128–130]. Although it is also true in the clinical setting, the toxicity, mainly nephrotoxicity, is lower when lipid formulations are used [117, 123, 131–139]. There is some evidence of greater effectiveness of the lipid formulations of amphotericin B in relation to amphotericin B deoxycholate. When used as induction therapy, L-AmB has

Table 2.1 Comparative characteristics of amphotericin B formulations

Characteristics	Amphotericin B deoxycholate	ABLCL	L-AmB
Structure	Micelle	Ribbon-like structures	Small spherical unilamellar lipid vesicles
Size (nm)	0.035	1600–11,000	Mean diameter: <100
Composition	Amph B deoxycholate	1:1 molar ratio of amph B/phospholipid (DMPC and DMPG)	HSPL, cholesterol, DSPG and amph B
Mode of action	It binds to ergosterol (fungal membrane) resulting in increased permeability, output of intracytoplasmic compounds and finally in fungal death	Release of amph B from complexes, possibly host macrophage- and phospholipase-mediated	Liposome targeting to fungal cell wall with release of amph B into the fungal cell
Nephrotoxicity	+++	++	+
Infusion-related toxicity	+++	++	+
Pharmacokinetic parameters (mean ± standard deviation)			
C _{max} (µg/mL) at steady state	1.1 ± 0.2	1.7 ± 0.8	83 ± 35.2
AUC _{0–24} (µg h/mL)	17.1 ± 5.0	14.0 ± 7.0	555 ± 311
Terminal elimination half-life (h)	91.1 ± 40.9	173.4 ± 78.0	6.8 ± 2.1
V _d (L/kg)	5.0 ± 2.8	131 ± 57.7	0.11 ± 0.08
Clearance (mL/h/kg)	38.0 ± 15.0	436 ± 188.5	11.0 ± 6.0
Distribution			
Protein binding, %	>95	>95	>95
CSF concentration relation to serum, %	0–4	3 (in animal)	<1
Urine concentration relation to serum, %	3–20	<5	4.5
Metabolism	Minor hepatic	Unk	Unk
Elimination	Feces	Unk	Unk
Comparative tissue concentrations of amphotericin formulations			
Liver	++	+++	+++
Spleen	+	+++	+++
Lung	+	++++	+
Kidney	+	±	+
Brain	–	±	±

Source: Data derived from [69, 81, 110–124]

ABLCL amphotericin lipid complex, *L-AmB* amphotericin B lipid complex, *HSPL* hydrogenated soy phosphatidylcholine, *DSPG* distearoyl-phosphatidylglycerol, *DMPC* dimyristoyl phosphatidylcholine, *DMPG* dimyristoyl phosphatidylglycerol, *C_{max}* maximum concentration of drug in serum, *C_{max}* peak drug concentration, *AUC* area under the concentration curve, *V_d* volume of distribution

Note: pharmacokinetic parameters after multiple doses of 0.6 mg/kg/day of amph B deoxycholate or 5 mg/kg/day of L-AmB or ABLCL

demonstrated faster culture conversion in cryptococcal meningitis, and was associated with improved survival and lower toxicity in AIDS patients with moderate to severe disseminated histoplasmosis in comparison to amph B deoxycholate [140, 141]. L-AmB (5 mg/kg/day) also showed superior clinical efficacy to amph B deoxycholate (1 mg/kg/day) in the treatment of neutropenia-associated invasive fungal infections [139].

Any of the lipid formulations of amph B are recommended by the IDSA guidelines for the treatment of non-neutropenic patients with suspected azole- and echinocandin-resistant candidemia, candida suppurative thrombophlebitis, candida endocarditis, and chronic disseminated (hepatosplenic) candidiasis. In addition, they proposed these drugs as an alternative treatment for candidemia in neutropenic and non-neutropenic patients, candida septic arthritis, or osteomyelitis, and as alternative empiric treatment of non-neutropenic patients in the intensive care unit with suspected invasive candidiasis and with intolerance to other antifungal drugs. The same guidelines recommend L-AmB for the initial treatment for central nervous system candidiasis and for candida chorioretinitis without vitritis due to fluconazole/voriconazole-resistant isolates. L-AmB is also suggested as an alternative treatment for central nervous system candidiasis in neonates [29].

For aspergillosis infections, the IDSA guidelines recommend amph B deoxycholate and lipid formulations as alternative treatments for initial or salvage therapy. This document also suggests lipid formulations for refractory and progressive aspergillosis or for empiric and preemptive therapy in allogeneic hematopoietic stem cell transplant recipients and patients treated for acute myelogenous leukemia with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy [35]. The IDSA guidelines also recommend lipid formulations of amph B instead of amph B deoxycholate for patients with cryptococcal meningitis with or predisposed to renal dysfunction and for the treatment of pulmonary, meningitis and disseminated sporotrichosis [30, 142].

2.1.2.1 Dosing

In general, for all fungal infections but CM, the recommended dose of lipid formulations of amphotericin B is 3–5 mg/kg daily for treatment and 1–3 mg/kg daily for prophylaxis. The dose for CM is 3–4 mg/kg per day of L-AmB and 5 mg/kg per day of ABLC, both of them with or without flucytosine, for at least 2 weeks [30, 143]. The pediatric dosing is 5 mg/kg/day of ABLC or L-AmB [144].

2.1.2.2 Adverse Events and Toxicity

In comparison with amph B deoxycholate, rates of infusion related acute reactions are similar with ABLC (60%) but lower with L-AmB (48%) [103, 117]. To reduce infusion-related reactions, it is recommended the use of low-dose hydrocortisone

(1 mg/kg), diphenhydramine (25–50 mg), meperidine (0.5 mg/kg), and nonsteroidal anti-inflammatory agents as premedication [118, 135, 145].

Numerous studies have shown that lipid formulations are less nephrotoxic than amph B deoxycholate. The Barrett et al.'s systematic review found that ABLC and L-AmB decreased all-cause risk of mortality and renal toxicity, compared with amph B deoxycholate [146]. Martino's systematic review also found that ABLC is significantly less nephrotoxic than amph B deoxycholate and can be administered securely to patients with preexisting renal injury [147]. L-AmB used in the treatment of fever in neutropenic patients with cancer showed similar efficacy but significantly less infusion-related reactions and nephrotoxicity than amph B deoxycholate [138]. In comparative trials, adverse events requiring discontinuation of the drug have occurred less frequently when patients received L-AmB (12%), followed by those receiving ABLC (32%) and amph B deoxycholate (44%) [103]. Wade et al. have also reported considerably lower rates of nephrotoxicity, infusion reactions and hypomagnesemia among patients with renal dysfunction and invasive fungal infections receiving L-AmB compared with those receiving ABLC [115].

L-AmB used in 33 consecutive patients at least 65 years old as empirical therapy for the treatment of invasive fungal infections showed equivalent safety and efficacy to those observed in younger patients, but higher incidence of severe hypokalemia when used for extended periods. The incidence of grade III or IV hypokalemia was similar in the older and younger groups [148]. A characteristic triad of acute infusion-related toxicity to L-AmB has been described. The following symptoms alone or in combination of 1 of 3 symptoms can be present: chest pain, dyspnea, and hypoxia; severe abdomen, flank or leg pain; and flushing and urticaria. These reactions occur within the first 5 min of infusion and disappear with administration of diphenhydramine. A multicenter analysis found a mean overall occurrence of 20% (range: 0–100%) of this specific toxicity among 64 centers [149].

2.2 Triazole Antifungal Agents

2.2.1 General Properties

Azoles are a group of antifungals of great importance in the treatment of systemic mycoses that share a common basic chemical structure and mechanism of action, inhibition of membrane sterol synthesis. A major change occurred with the identification of increased antifungal activity of the N substitution in the imidazole ring, which led to the development of current triazoles.

A first generation of triazoles were developed in the eighties and have been in clinical use since then, with limited (itraconazole) or no activity (fluconazole) against filamentous fungi. A second generation of drugs developed in late nineties and more recently is now available (voriconazole, posaconazole, isavuconazole), with improved activity against *Aspergillus* and other filamentous

fungi. Clinical studies have shown their effectiveness in the management of multiple fungal infections.

Triazoles are widely used due to their broad spectrum of antifungal activity, availability of both IV and oral formulations, and safety profile. It is expected that in the future newer agents and more indications will be identified [150, 151].

2.2.1.1 Chemical Structure

The imidazole nucleus is a 5-atom heterocyclic structure with 3 C and 2 N (see Fig. 2.2). This structure is present in nitroimidazoles, utilized in antianaerobic and antiparasitic therapy (metronidazole), and azole antifungals (clotrimazole, miconazole, ketoconazole), currently used for local therapy of superficial infections. The substitution of a C for an N atom originates the term “triazoles” (three N atoms in the ring), and it is associated with significant changes in the antifungal activity and pharmacokinetic properties in relation to older azoles (i.e. ketoconazole). The triazoles have a more specific binding to fungal enzymes than to mammal enzymes for sterol synthesis, more potent antifungal activity, and broader spectrum, less metabolic side effects, and better bioavailability and tissue distribution than older azoles.

2.2.1.2 Mechanism of Action

The structural target for triazoles in the fungal cell is the cellular membrane. Action at this level explains part of older azoles limitations, since their activity would not be completely specific for fungal organisms. Older azoles have also some inhibitory activity on steroid metabolism in mammalian cells; for example, ketoconazole was used in the management of primary Cushing syndrome because of its significant inhibition of corticoid synthesis [157].

Triazoles are inhibitors of the enzyme lanosterol 14- α -demethylase, coded by the gene CYP51A, involved in the synthesis of ergosterol. This enzyme catalyzes the oxidative elimination of 14-methyl group from fungal cell lanosterol (monooxygenase P450 activity). Its inhibition causes the accumulation of lanosterol precursors (methyl-sterols) and changes the proper composition of the cell membrane, which produce structural and functional consequences (lanosterol deficiency and decreased membrane fluidity), primarily in cellular reproduction and death. Triazoles block the activity of the enzyme by binding to the active site, and their increased affinity to this site due to the third N atom present in the imidazole ring produces higher antifungal activity [158].

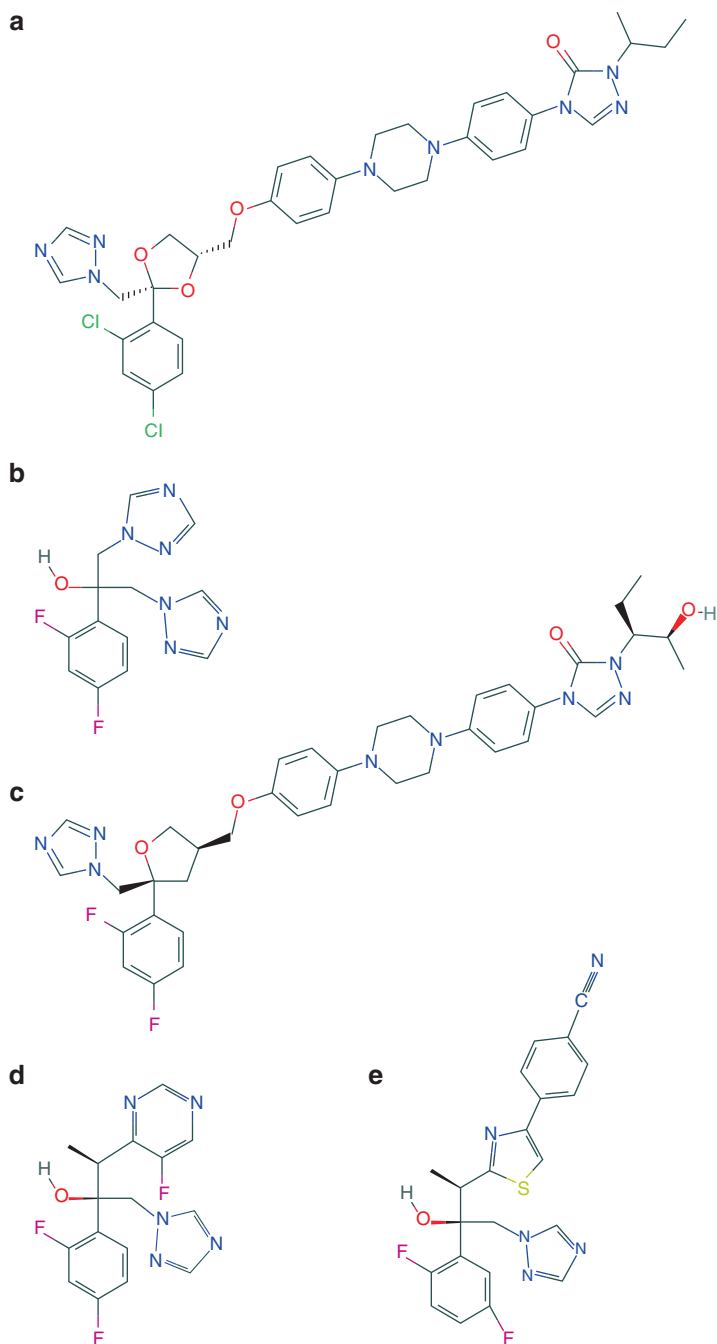


Fig. 2.2 Chemical structure of triazoles. (a) Itraconazole, (b) Fluconazole, (c) Posaconazole, (d) Voriconazole, and (e) Isavuconazole. Source: References [152–156]

2.2.1.3 Pharmacokinetics

Main pharmacokinetic characteristics of triazoles are displayed in Table 2.2. In summary, these drugs have good oral absorption (with special ingestion requirements for certain formulations of itraconazole and posaconazole), a prolonged half-life (which allows once or twice daily dosing regimens in most cases), good distribution in body tissues with clinical use in different types of invasive disease, and are available in both oral and parenteral formulations [160].

Fluconazole and voriconazole reach higher concentrations in tissues because of their smaller molecular size. Fluconazole shows better concentration in cerebrospinal fluid, and all azoles reach good concentrations in brain tissue. Posaconazole reaches the highest concentration in alveolar cells and voriconazole in bone tissue. Triazoles concentrate similarly well in liver and kidneys [113].

Due to a less predictable absorption, interactions with other drugs, and subject variability of metabolism, therapeutic drug monitoring is recommended to optimize regimens and minimize side effects for itraconazole, voriconazole, and posaconazole [161–163]. Trough levels should be tested within 30 min before patient dosing. The recommended target trough plasma levels for triazoles and their recommended day of testing after initiation of therapy are shown in Table 2.3.

2.2.1.4 Spectrum of Activity and Resistance

All members in the class show good activity against most *Candida* species. Fluconazole is effective against most clinically significant *Candida* sp. and against *Cryptococcus* sp., and to a lesser extent against most dimorphic endemic fungi (*Histoplasma*, *Blastomyces*, *Coccidioides*, and *Paracoccidioides* spp). Itraconazole has a broader spectrum that includes *Sporothrix schenckii*, *Aspergillus* spp. and some other filamentous fungi such as dematiaceous fungi and mucorales. Its mold activity is lower than newer triazoles. Voriconazole is active against dose-dependent and fluconazole-resistant *Candida* species (*C. glabrata* and *C. krusei*, respectively). It also shows increased activity against molds, particularly *Aspergillus* spp., *Fusarium* spp., *S. apiospermum*, and dematiaceous fungi. Posaconazole and isavuconazole add to voriconazole spectrum their activity against Mucorales [167, 168].

Resistance to triazoles is well described. Mechanisms of acquisition of resistance include overexpression with increased activity of efflux pumps (ATP binding cassette, ATP and major facilitator superfamily -MFS), and point mutations that cause changes in tridimensional structure or activity of C-14 α demethylase [169]. The point mutations cause structural changes in the active site of the demethylase, decreasing the affinity to its ligands. *Candida* species can be intrinsically resistant as is *C. krusei* to fluconazole, show dose-dependent susceptibility as *C. glabrata* versus fluconazole or acquire resistance like *C. albicans* to azoles, largely by changes in the activity of efflux pumps.

Aspergillus resistance to triazoles with mold activity has also been reported in some places. Specific alterations in coding regions of the enzyme in the CYP51A

Table 2.2 Main pharmacologic characteristics of triazoles in clinical use

Characteristics	Itraconazole	Fluconazole	Voriconazole	Posaconazole	Isavuconazole
MW	705.6	306.2	349.3	700.7	814 ^a
Half-life (h)	19–22	27–34	6	20–30	56–77
Plasma protein binding (%)	>95	11–22	58	98	>99
Oral bioavailability (%)	55 (capsule with food)	>80	96	See text	98
Volume of distribution (L/kg)	796	46	1.2–4.6	1774	450
Liver failure dose adjustment	Yes	No	Yes	No	No
Metabolism	Liver		Liver	Liver (limited proportion)	Liver
Elimination	Feces	Kidney (60–75% unchanged)	Kidney (2% unchanged)	Feces (mostly unchanged)	Feces
Kidney failure dose adjustment	No	Yes	No (oral)	No	No
Therapeutic drug monitoring	Recommended		Recommended	Recommended	
Most significant toxicities	Nausea, gastrointestinal symptoms	ALT elevation (10%)	Visual disturbances, photosensitivity, confusion	Gastrointestinal symptoms, headache	Gastrointestinal symptoms
Comparative tissue concentrations of triazoles					
Liver	+	+	++	ND	ND
Spleen	+	++	+	ND	ND
Lung	+	+	+	++	ND
Kidney	+	+	+	ND	ND
Brain	+	++	+	+	ND

Source: References [113, 150, 151, 159]
ND No data
^aMW (Molecular Weight) of isavuconazonium

Table 2.3 Recommended target trough plasma levels for triazoles

Antifungal drug	Target concentration during prophylaxis mg/L	Target concentration during treatment of IFD mg/L	Day of test after initiation of drug
Itraconazole	>0.5	>1	>7 days
Voriconazole*	>1	1–5.5	After 3–5 days
Posaconazole	>0.35 after the first 48 h ≥0.9 after day 7**	>1.8	>7 days

Source: Data from [161, 164–166]

IFD invasive fungal disease

aIrrespective of formulation

bFor the tablet and intravenous formulations TDM is not required when they are used for prophylaxis, as target levels are anticipated to be reached in nearly all the patients

gene have been associated in some cases with itraconazole and posaconazole resistance and with cross-resistance to all triazoles [170].

Identification of triazole resistance is increasingly available with standardization of methods, identification of clinically relevant breakpoints, and consensus from major international institutions (CLSI, EUCAST) in recent years [171].

2.2.1.5 Clinical Utility

Triazoles have a wide spectrum antifungal activity, which includes both yeast and filamentous fungi. Much more limited in the case of the older generation, but with significant increase of activity in the case of the newer products, such as posaconazole and voriconazole.

Fluconazole continues to be of major importance in the management of different clinical presentations of candidiasis in multiple groups of patients [168], and for consolidation treatment of cryptococcosis. Itraconazole is recommended in the management of dimorphic fungi and to some extent in filamentous organisms.

Voriconazole, posaconazole, and isavuconazole have evolving roles in the management of severe fungal infections by filamentous organisms in the most immunosuppressed individuals. Voriconazole is considered a first choice for invasive aspergillosis in most clinical situations. Posaconazole has been used preferentially in antifungal prophylaxis and *Mucor* infections, and isavuconazole has shown high efficacy in the treatment of aspergillosis and *Mucorales* [172].

2.2.1.6 Adverse Events and Drug Interactions

Compared to older azoles (i.e. ketoconazole), currently available drugs show much lesser hormonal inhibition, gastrointestinal side effects, and hepatotoxicity. Triazoles as a group are deemed relatively safe drugs.

Itraconazole most commonly causes nausea (10%) and gastrointestinal symptoms (diarrhea, 8%; vomiting, 6%; abdominal discomfort, 6%). Hyperbilirubinemia and liver enzyme elevation is reported in about 5% [173].

Fluconazole used at doses higher than 400 mg/day can cause headache in 2%, anorexia in 3% of patients and transient ALT elevation in 10% of patients.

Reversible visual disturbances (30%), photosensitivity (20%), hallucinations and confusion (15%) have been described with voriconazole use. Recent reports have associated presentation of skin cancer in immune-suppressed patients with use of voriconazole, which needs further clarification [174, 175].

Side effect profile of posaconazole is very similar to that of fluconazole. Experience with isavuconazole in clinical trials has shown that it is largely well tolerated.

Prolongation of the QTc has been observed with triazoles, including posaconazole [176, 177], and this can cause sudden death. The I_{Kr} channel, one of the membrane channels responsible for potassium outflux movement, is inhibited by fluconazole and other triazoles. This inhibition is associated to ventricular repolarization changes that increase vulnerability to cardiac arrhythmias. Patients with other drugs that can cause QTc prolongation, severe bradycardia, hypokalemia, or hypomagnesemia should be cautiously prescribed when used concomitantly with azoles. Contrary to other drugs in the group, isavuconazole has been associated with QTc shortening, of unclear clinical significance.

Triazoles present a significant number of drug interactions [178, 179]. Interactions with immunosuppressants, rifamycins, anticonvulsants, omeprazole, warfarin, statins, and antiretrovirals, amongst others, are particularly important. See Table 2.4 [181].

Interactions of triazole antifungals can be divided into the following categories: modifications of antifungal pharmacokinetics by other drugs, modifications of other drug pharmacokinetics by antifungals, and two-way interactions. The mechanisms involved include azole inhibition of drug metabolizing enzyme cytochrome (CYP) P450 isozymes, such as CYP3A4/5, CYP2C9 and CYP2C19 in varying degrees [182]. Triazoles can also inhibit drug transporter P-glycoprotein (P-gp) within the gastro-intestinal tract and the liver, for which immunosuppressants are substrates.

The degree of these interactions varies greatly, as azole inhibition of relevant enzymes can be dose-dependent and differs in potency and selectivity. Itraconazole and voriconazole are reported to be more potent inhibitors of CYP3A4 than posaconazole and fluconazole. In terms of inhibition of P-gp, itraconazole and posaconazole have the more significant activity [183].

Triazoles are used frequently in transplant patients, either for prevention or treatment of suspected or proven fungal infections, and can interfere with the metabolism and transport of immunosuppressants (i.e. cyclosporine, tacrolimus, sirolimus, and everolimus), which are drugs of narrow therapeutic margin.

Triazoles can increase exposure to immunosuppressant, consequently increasing risk for side effects of these drugs. On the other hand, discontinuation of azoles without dose adjustment of the immunosuppressant drugs may lead to sub-therapeutic immunosuppressant exposure and risk of transplant rejection or graft-versus-host-disease.

Table 2.4 Recommendations for selected drug interactions of triazoles

Drug	Itraconazole	Fluconazole	Voriconazole	Posaconazole	Isavuconazole
Antacids	Avoid				
Atazanavir				Monitor for atazanavir toxicity	
Atorvastatin	Monitor for atorvastatin toxicity				
Carbamazepine			Avoid		Avoid
Cyclosporin A	Monitor for CsA toxicity	Monitor for CsA toxicity	Monitor for CsA toxicity	Monitor for CsA toxicity	Use with caution
Efavirenz	Avoid		Efavirenz dose reduction	Increase dose of posaconazole if need as per therapeutic drug monitoring	
Midazolam	Monitor for midazolam toxicity	Monitor for midazolam toxicity	Monitor for midazolam toxicity	Monitor for midazolam toxicity	
Omeprazole	Avoid capsules, use solution	Omeprazole AUC increased >100%, consider omeprazole dose reduction	Omeprazole AUC increased >100%, consider omeprazole dose reduction		
Phenytoin	Avoid	Monitor for phenytoin toxicity		Avoid	
HIV protease inhibitors (other than atazanavir)	Avoid higher doses of itraconazole		Avoid		
Rifampin	Avoid	Consider fluconazole dose increase	Avoid		Avoid
Sirolimus			Avoid	Avoid	Use with caution
Tacrolimus	Monitor for tacrolimus toxicity	Monitor for tacrolimus toxicity	Monitor for tacrolimus toxicity	Monitor for tacrolimus toxicity	Use with caution

Source: Data from [178–180]

As a potent inducer of CYP enzymes, rifampin significantly increases the metabolism of azoles. Concomitant use of rifampin with itraconazole, voriconazole, or isavuconazole should be avoided, and consideration to increasing fluconazole dosing is required if concomitant use is necessary [184].

In the management of HIV-infected patients, fungal infections are frequent and important complications. Efavirenz should not be coadministered with itraconazole or posaconazole. Voriconazole and itraconazole doses >200 mg/day are not advised in patients receiving protease inhibitors. Posaconazole can increase >100% AUC of atazanavir (boosted or unboosted). Fluconazole use does not generally require adjustment of dosing and can be used with most antiretrovirals [181].

2.2.1.7 Dosing and Administration. Use in Special Populations

Dosing criteria for triazoles are already established for general use in adult populations. However, the newer drugs (posaconazole, isavuconazole) still miss clinical pharmacokinetic data for groups of patients such as neonates, younger children, and pregnant women.

Neonates and Children As more experience is accumulated, use of older triazoles in children is recommended for their routine indications [185, 186]. FDA labeling of voriconazole and posaconazole still restricts their use to older children [187]. In spite of being an older drug, itraconazole has not been developed for pediatric use and does not have formal indications [188]. Recommendations for the use of triazoles in the management of aspergillosis are similar in children and adults, although recognizing that doses of voriconazole are higher in younger children (<12 years) and in younger adolescents with a weight < 40 kg. In these patients, loading dose is 9 mg/kg twice, followed by 4–8 mg/kg (higher dose for invasive molds and more serious infections) [35, 189].

Pregnant Women According with the FDA classification of drugs and risk category in pregnancy, fluconazole status varies with the dose used. It is considered C when a single 150 mg-dose is indicated, but is D for higher doses. This is based on observation of birth defects in five children exposed in utero to fluconazole, and animal experiments showing teratogenic potential. Fluconazole remains contraindicated in pregnancy with the exception of the lower dose. Itraconazole, isavuconazole and posaconazole are currently classified as category C, while voriconazole is in category D. Current consensus is to restrict use of triazoles in pregnancy, in particular in the first trimester [190].

Renal Failure Dose adjustment is recommended for fluconazole. Daily dose should be reduced by 50% with a creatinine clearance lower than 50 mL/min. For end-stage renal disease patients (ESRD) on hemodialysis (HD) dose is normal and goes after dialysis. Parenteral voriconazole preparation with cyclodextrin is not recommended in renal failure due to potential accumulation and toxicity of cyclodextrin. Patients who are already on some form of renal replacement therapy do not

have any concern as cyclodextrin is efficiently removed by dialysis. Because cyclodextrin contained in Itraconazole oral solution is metabolized by amylase, patients with renal failure can use it without dose adjustment [191].

Liver Failure Voriconazole has more extensive liver metabolism and in moderate to severe liver failure, its maintenance dose should be reduced to 50% after a regular loading regimen.

Obesity Fluconazole should be dosed by total body weight to achieve AUC/MIC ratios that have been associated with better outcomes. Posaconazole dose should not be corrected for increased body weight. This has still to be evaluated for the newer formulations (tablet, IV solution). Voriconazole dosing using total body weight can reach supratherapeutic concentrations. Its dose should not be changed for increased body weight or BMI in the case of oral voriconazole. Until further studies are performed, use of either the adjusted body weight or ideal body weight when dosing weight-based IV voriconazole could be justified [192].

2.2.2 Individual Agents

2.2.2.1 Itraconazole

Itraconazole is available as a 100 mg capsule and an oral suspension in cyclodextrin (100 mg/10 mL). Cyclodextrin makes itraconazole soluble and enhances its absorption. Oral absorption of the capsule depends on food intake, although absorption of the solution is best on an empty stomach. Interestingly, coadministration with a cola beverage increases the AUC of the capsule formulation. Absorption of the capsule is decreased with hypochlorhydria, mucositis, and graft-versus-host intestinal changes, conditions that can be present in AIDS patients or bone marrow transplant recipients.

Therapeutic drug monitoring is useful to adjust proper dosing, taking in consideration the method used for adequate interpretation. Tissue, pus and bronchial secretion concentrations of itraconazole are higher than plasma levels. The drug is metabolized in the liver and excreted in feces; prolonging its half-life in cirrhosis. When administered via oral, minimal amount of active itraconazole is eliminated in urine with most of cyclodextrin (>99%) excreted intact in feces.

Itraconazole most frequent side effects are nausea and abdominal discomfort. Frequency of gastrointestinal symptoms is higher with the solution presentation (osmotic effect). Hypokalemia and edema can be seen with higher doses. Itraconazole is contraindicated in pregnancy and in nursing mothers.

Itraconazole is useful in the treatment of dimorphic organisms (*Blastomyces* spp., *Histoplasma* sp., *Coccidioides* spp., *Paracoccidioides* spp., *Sporothrix* spp.), especially in less severe forms, less immunocompromised individuals or as consolidation treatment. Because activity against *Aspergillus* is lower in comparison to newer agents (second generation), indications of itraconazole in aspergillosis are more limited. It is indicated for the management of allergic

bronchopulmonary aspergillosis or as an alternative therapy in aspergilloma [35]. Other uses include phaeohyphomycosis, ringworm, onychomycosis, tinea versicolor, and occasionally candidiasis.

Usual daily dose for cutaneous conditions, including sporotrichosis, is 200 mg. An initial loading dose of 200 mg tid for the first 3 days when used in the treatment of deep mycoses is recommended to ensure adequate serum and tissue levels in the short term. Recommended dose for treatment of invasive mycoses, selected forms of aspergillosis or prophylaxis of invasive aspergillosis is 400 mg daily, divided every 12 h.

2.2.2.2 Fluconazole

Fluconazole is an imidazole analogue to ketoconazole with more specific fungal sterol synthesis inhibition and increased antifungal activity. It has good bioavailability (>90%), which is a significant difference with itraconazole, good distribution in fluids and tissues, long serum half-life (approximately 30 h), and relatively low (11–12%) binding to plasma proteins. Its elimination is mostly renal. The molecule has a second triazole ring that decreases lipophilicity and increases unbound drug in blood.

Fluconazole for systemic use is available in capsules, tablet, powder for oral suspension, and injectable form for IV infusion at a concentration of 2 mg/mL. Tolerance to fluconazole is considered good. Liver toxicity is a concern, especially when higher doses are used for treatment of cryptococcosis or disseminated candidiasis.

Fluconazole is active against yeasts and inactive against molds. It can be used to treat mucosal candidiasis (oro-pharyngeal, esophageal, vaginal), disseminated and invasive candidiasis, cryptococcosis, and systemic dimorphic mycoses (histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, and sporotrichosis). Depending on the disease severity, immunologic status or comorbidities of the patient, and availability of other antifungals, fluconazole can be an initial treatment, or a consolidation phase treatment in these indications [193].

Fluconazole has had an important role in the management of serious forms of infection by *Candida* [194], although this role is changing in recent years with newer recommendations favoring use of echinocandins in most seriously ill patients [29, 195, 196]. In the case of invasive candidiasis and candidemia, fluconazole should be considered for patients not critically ill and infected by fluconazole-sensitive organisms, using a loading dose of 800 mg followed by 400 mg daily [29, 195]. In the treatment of mucosal candidiasis, lower doses of fluconazole are appropriate. A single 150 mg is indicated for vulvo-vaginal candidiasis, and daily doses of 100 mg are used for oro-pharyngeal and esophageal candidiasis.

Fluconazole at doses of 800 mg/day combined with amphotericin B is recommended as an alternative regimen for induction treatment in cryptococcal meningitis or disseminated disease in HIV patients when flucytosine is not available. In these patients, doses of 400 or 200 mg daily are used in the consolidation and maintenance phases respectively [30]. Dose of 400 mg daily of fluconazole are recommended as initial

antifungal treatment of immunosuppressed and immunocompetent patients with mild-to-moderate pulmonary cryptococcosis [30].

2.2.2.3 Voriconazole

Voriconazole is a second generation triazole that was approved for clinical use in 2002. In voriconazole, the second triazole ring has been replaced with a fluoropyrimidine nucleus, which explains its broader spectrum. The main advantage of Voriconazole over first-generation triazoles is its activity against filamentous fungi, including *Aspergillus* sp., *Fusarium* spp., and *S. apiospermium* [197–199]. Despite its broad-spectrum activity against yeast and molds, voriconazole is not active against Mucorales.

Currently, voriconazole is considered the drug of choice for the treatment of invasive aspergillosis [35, 200]. Reported clinical experience shows some promising results with combination of voriconazole and echinocandins as a rescue regimen [201–204].

Voriconazole is available for oral and parenteral use. It should be taken with empty stomach because food and high content of fat decrease Voriconazole absorption, reducing bioavailability in 20%. Half-life is 6 h, requiring twice daily administration. Parenteral formulation of voriconazole also contains cyclodextrin, which could accumulate in renal failure. Its use in patients with renal impairment should be individualized.

In general, voriconazole is well tolerated. Reversible disturbances in vision (impaired color discrimination, blurring, and photophobia) is reported in about 25–30% of patients and are not seen with other triazoles. Skin rashes, photosensitivity, facial erythema, hallucinations and confusion are other significant side effects. Periostitis has been associated to prolonged use, and serious EKG alterations (torsade de pointes, QTc prolongation) have occurred in patients with predisposing factors to arrhythmia.

For invasive aspergillosis and serious mold infections, a loading dose of 6 mg/kg twice daily is recommended in the first day, followed by 4 mg/kg bid. For the treatment of invasive *Candida* infections dose should be lower, at 3 mg/kg bid. Oral dosing (tablets) is 400 mg bid the first day and then 200 mg bid for persons of >40 kg. For persons under 40 kg, the recommended dose is 200 mg bid for the first day, followed by 100 mg bid. Intake should be 1 h apart from meals.

2.2.2.4 Posaconazole

This triazole has a broad spectrum of antifungal activity, including *Aspergillus* and *Candida* [167]. It can be considered a derivative of itraconazole with structural modifications that enhance its activity and tissue concentration (lipophilic molecule with high concentration in tissues). Oral absorption and bioavailability of posaconazole suspension are difficult to predict, because they are significantly affected by factors like meal ingestion or presence of mucosal lesions in the gastrointestinal

tract [205–207]. Posaconazole suspension should be taken with high-fat meals to enhance absorption. Although its half-life is long and suggests the possibility of once daily dosing, AUC is higher with bid or tid dosing, which is recommended for the oral suspension.

The newer delayed-release tablet has better absorption, improved bioavailability, and a fourfold increase in maximum concentration, a threefold increase of the area under the curve, and more prolonged presence in plasma. In contrast to the suspension, the effect of food or drugs that may alter gastric acidity is moderate. Additionally, patient intervariability is reduced. All this favorable pharmacokinetic changes allow for once daily dosing [161, 208, 209].

Posaconazole is usually well tolerated. In clinical trials the most common side effects have been gastrointestinal symptoms including nausea and abdominal pain. Initially available only for oral administration, its indications have been mainly referred to prophylaxis of fungal infection in patients at high risk (prolonged neutropenia, acute myeloid leukemia, post-transplant), in particular for filamentous fungal complications [210, 211]. The oral suspension has been evaluated for refractory aspergillosis at a daily dose of 800 mg with a 42% rate of global response [212]. Currently, a formulation for parenteral administration is also available and undergoing phase III clinical trial in the treatment of invasive aspergillosis, with completion estimated for July 2018 [213].

Posaconazole has good activity against *Mucor* spp. and has a role in the treatment of mucormycosis in combination with surgical procedures, usually after an initial period with amphotericin B [214].

Oral suspension and delayed-release tablet have different dosing regimens. The dose of the suspension is 200 mg tid with food for prophylaxis or 400 mg bid with meals when indicated for treatment [215–217], while the 300 mg tablet is administered once a day. Intravenous dosing of 300 mg daily is approved for prophylaxis.

2.2.2.5 Isavuconazole

It is the newest member of the second-generation triazole antifungal approved by the US FDA [159, 168, 180]. It has been approved for the treatment of both invasive aspergillosis and invasive mucormycosis [218]. It is also under investigation for the treatment of candidemia and invasive candidiasis, cryptococcosis, and dimorphic fungi [219].

Isavuconazole is administered as the hydrosoluble prodrug isavuconazonium, which is available in tablets and for parenteral administration. In preclinical and clinical studies, it has shown significant antifungal potency against a broad range of yeasts, dimorphic fungi, and molds. Isavuconazole has a broad spectrum of antifungal activity, similar to amphotericin B.

Clinical experience so far has revealed that isavuconazole may be associated with less toxicity than voriconazole, even when administered without therapeutic drug monitoring. Additionally, the oral formulation is highly bioavailable and the parenteral presentation is b-cyclodextrin-free (due in large part to the presence of aromatic

moieties in the molecule). These are interesting properties that will increase interest on isavuconazole as a new addition to the triazole class of antifungals. Isavuconazole dosing is similar when administered either intravenously or orally. In both cases, the loading dose is 200 mg every 8 h for six times, followed by 200 mg daily.

2.2.3 *Newer and Investigational Agents: Efinaconazole, Albaconazole, Ravuconazole and Others*

A numerous group of newer triazole molecules are currently under different stages of development [220]. Preliminary clinical studies are already available for ravuconazole, albaconazole, and efinaconazole (available as a topical agent).

Ravuconazole is related to fluconazole and voriconazole. It has activity against yeasts (*Candida* spp. and *Cryptococcus* spp.), dimorphic fungi and filamentous organisms (demateciosus, mucorales). It is not active in vitro against *Fusarium* spp. Clinical studies for onychomycosis have been reported with a mycological cure rate of 59% and clinical response of 56% [221]. It is still to be determined what potential indications may have and what results are obtained in clinical trials for systemic mycoses.

Albaconazole shows low MICs against *Candida* spp. and has been clinically studied in the treatment of vulvo-vaginal candidiasis and onychomycosis, and experimentally against *S. proliferans*. Its long half-life allows for weekly dosing.

Efinaconazole is a potent antifungal drug against *T. rubrum*, *T. mentagrophytes* and *C. albicans*, approved in 2014 for the treatment of onychomycosis. It also has activity against other species of fungus, including some nondermatophytes molds (*Acremonium* spp., *Fusarium* spp., *Paecilomyces* spp., *Pseudallescheria* spp., *Scopulariopsis* spp., and *Aspergillus* spp.), *Cryptococcus* spp., *Trichosporon* spp., and other species of *Candida* different to *C. albicans* [222].

The list of newer compounds includes RI26638, KP103, T8581, TAK187, FX0685, ZJ522, TAK456, Syn2869, and additional molecular modifications for dioxantriazoles, triazole-quinoxalines, and triazole-benzimidazoles.

The search for newer clinically active compounds might lead to the availability of triazole derivatives with increased antifungal spectrum and effectiveness, as well as better tolerance.

2.3 Echinocandins

Echinocandins are the newest members of the antifungal armamentarium and the first ones targeting the fungal cell wall [223, 224]. Currently, three semi-synthetic echinocandin derivatives have received FDA approval for clinical use: caspofungin (2001), micafungin (2005), and anidulafungin (2006). A fourth compound, the CD101, is under development.

2.3.1 Chemical Structure

Echinocandins are semisynthetic lipopeptides antibiotics, composed of cyclic hexapeptides with modified N-linked acyl lipid side chains [225, 226] (Fig. 2.3).

2.3.2 Mechanism of Action

Echinocandins competitively inhibit the beta-1,3-D-glucan synthesis, a polysaccharide which is an essential component of the fungal cell wall of many fungi. Beta-glucans represent between 30 and 60% of the cell wall mass in yeasts, and its depletion results in fungicidal activity for *Candida* spp. and fungistatic effect for *Aspergillus* spp. [230, 231]. This mechanism of action is different from the one of other drugs, allowing a potential use of echinocandins in combination therapy [232], and because the target of echinocandins is unique to fungi, then absent in human cell, these drugs cause less toxicity and have fewer drug–drug interactions. In addition, some evidence from in vitro studies and murine models supports an immunomodulatory effect of echinocandins. They can unmask highly antigenic epitopes and amplify the host immune response [233].

2.3.3 Pharmacokinetics and Pharmacodynamics

Although pharmacokinetic and pharmacodynamic characteristics of echinocandins are similar, they differ in dosing, metabolic elimination pathways, and drug interaction profile. Like other large lipopeptide antibiotics, these drugs are poorly absorbed through the gastrointestinal system and must be administered by intravenous infusion. Due to their long half-life (10–26 h), they are dosed once daily, and because echinocandins are highly bound to plasma proteins, administration of a loading dose is recommended for caspofungin and anidulafungin, although it is not yet clear for micafungin. Also, high binding to plasma protein limit distribution of echinocandins to the cerebrospinal fluid and the eye, making them inadequate treatment for infections of these compartments [234–236].

Echinocandins are primarily eliminated through nonmicrosomal metabolism nonenzymatic degradation to inactive products, and then their urinary concentration is very low [234, 237]. They are not significantly metabolized by the cytochrome P450 enzymes nor are they substrates or inhibitors of P-glycoprotein pumps. As consequence, they have less drug–drug interactions in comparison with others antifungal drugs. However, caspofungin must be used with caution when severely impaired hepatic function is present.

Caspofungin shows a net terminal half-life of 27–50 h, and degrades spontaneously and is metabolized via hydrolysis and N-acetylation to two inactive

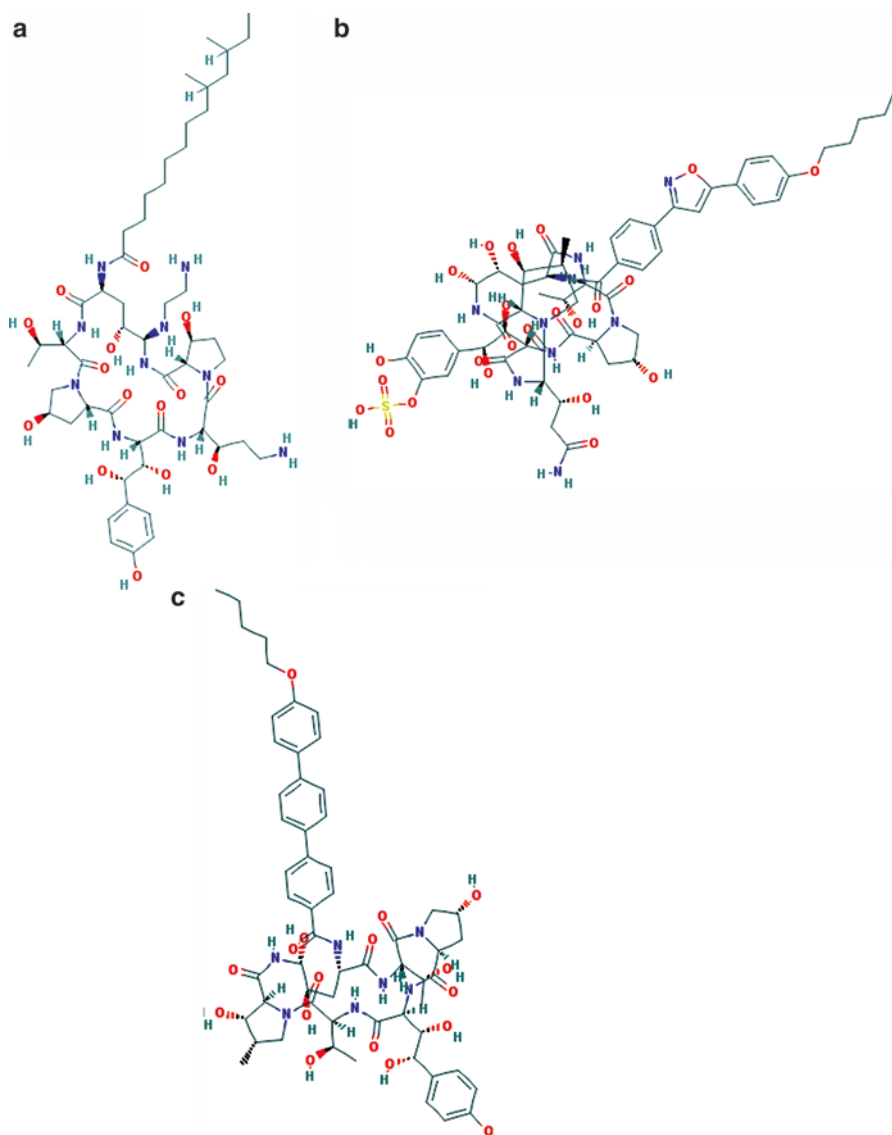


Fig. 2.3 Chemical structure of Echinocandins (a) Caspofungin, (b) Micafungin, and (c) Anidulafungin. Source: References [227–229]

metabolites; micafungin has a terminal half-life of approximately 15 h in adults, and is metabolized hepatically by arylsulfatase, catechol *O*-methyltransferase, and hydroxylation; while anidulafungin shows a terminal half-life of 40–50 h, and is not metabolized but instead eliminated by slow spontaneous degradation. All three echinocandins are nondialyzable, and their breakdown products are excreted predominantly by the fecal route, with only low concentrations of active drugs excreted by urine (less than 2%) [226, 231, 238].

In vitro studies showed that the fungicidal effect of echinocandins against *Candida* spp. is proportional to the maximum plasma drug concentration, that this effect persist after falling of drug concentration below MICs, and that it seems to correlate with the area under time-concentration curve to MIC ratio [237, 239]. However, similar information related to killing or inhibition of *Aspergillus* spp. is not completely defined yet [239, 240]. In addition, there are not established strategies to conduct therapeutic drug monitoring for echinocandins [237, 239].

2.3.4 Spectrum of Activity and Resistance

Because echinocandins show a similar spectrum of activity, they could be interchangeable specially when treating candidiasis infections. They have potent activity against many *Candida* spp. (*C. albicans*, *C. glabrata*, *C. dubliniensis*, *C. tropicalis*, and *C. krusei*), and although MICs against *C. parapsilosis* and *C. guilliermondii* are often higher, they are useful drugs against these candida species [241, 242]. The fungicidal activity against *Candida* spp., including fluconazole-resistant *C. glabrata* and *C. krusei*, is the main advantage of echinocandins [226].

Even though echinocandins inhibit growth of *Aspergillus* species at very low echinocandin levels, their activity against *Aspergillus* spp. is only fungistatic [223, 243–245], this is explained because in *Aspergillus* species, higher activity of cell wall remodeling and beta-glucan synthase is localized in apical and sub-apical branching points. In guinea pig models, echinocandins seem to potentiate the activity of triazoles against *Aspergillus* spp. [219, 246].

Although beta-1,3-D-glucan synthase from *Cryptococcus* spp. is highly inhibited by caspofungin, echinocandins have not activity against *C. neoformans* and *Cryptococcus gattii*, neither against *Trichosporon* spp. [225, 226]. Echinocandins are not effective drugs to treat mycosis produced by endemic dimorphic fungi (*Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Coccidioides* spp.), due to their modest activity against the mycelial phase of them. In addition, echinocandins have not significant activity against non-*Aspergillus* molds (Mucorales, *Fusarium* spp., or *Scedosporium* spp.) [226, 247–249], and only modest in vitro activity, without clinical utility, for some phaeohyphomycetes [250, 251]. Echinocandins are effective agents for prophylaxis of *Pneumocystis jirovecii* pneumonia although less effective for established pneumonia in experimental models [252, 253].

In contrast with what happens with amphotericin B and triazoles, activity of echinocandins are not affected by presence of biofilm; echinocandins MICs are

minimally affected when tested under biofilm conditions. *C. albicans* inoculum embedded in biofilm is almost completely cleared at the usual echinocandin serum levels [254, 255]. When evaluating activity against *C. tropicalis* biofilm, micafungin showed high activity while liposomal amphotericin B performed poorly [256]. This unique characteristic of echinocandins makes them particularly useful for the treatment of prosthetic device and catheter-associated infections.

Overall resistance to echinocandins of *Candida* spp. has been reported in up to 4%, and results from mutations in conserved regions of the gene-encoding glucan synthase (FK1 and FK2) [257, 258], and resistance to echinocandins has been documented for *C. albicans*, *C. glabrata*, *C. lusitaniae*, *C. tropicalis*, and *C. parapsilosis* [259, 260]. Previous exposure to an echinocandin had been associated with echinocandin resistance on multivariate analysis [254].

Resistance of *C. glabrata* is of particular concern, because it is now reported from around the world, at rates between 3 and 15%, and because isolation of strains with resistance to fluconazole and voriconazole and to echinocandins [259, 261–264]. Among the 162 fluconazole-resistant *C. glabrata* strains isolated between 2006 and 2010 in the US, resistance to any echinocandin was demonstrated in 18 (11%), while there was no resistance to echinocandins among 110 fluconazole-resistant strains isolated between 2001 and 2004 [262]. All the 18 resistant isolates contained an FKS1 or FKS2 mutation.

Resistance to echinocandins is associated with treatment failure and relapse or recurrence if there was an initial response and with higher rates of mortality at days 14 and 30 [261, 265, 266].

In an organ transplant recipient with persistent candidemia, Imbert and colleagues demonstrated that switching from both azole and echinocandin therapy to liposomal amphotericin B, produced that resistant *C. glabrata* isolate lost the FKS2 S663P alteration, regaining full susceptibility to echinocandin, while maintaining their pan-azole resistance. Based on this observation, authors suggest that more restricted use and/or a discontinuous administration of echinocandins may limit the spread of clinical resistance to these drugs [267].

2.3.5 Clinical Uses

Echinocandins are extensively used for prevention and empiric treatment of fungal infection, and for treatment of invasive candidiasis, especially in critically ill and neutropenic patients. The three echinocandins have FDA approval for the treatment of esophageal candidiasis and invasive candidiasis in adults. Micafungin has FDA approval to be used as prophylaxis of *Candida* infections in hematopoietic cell transplanted adults, while caspofungin is approved as empiric treatment for neutropenia febrile, and for esophageal candidiasis and invasive candidiasis in children older than 3 months [29, 268, 269]. Echinocandins had demonstrated improved survival when compared to amphotericin B and triazoles in the treatment of candidemia and invasive candidiasis [191, 270, 271] and, similar efficacy to amphotericin

B and fluconazole in the treatment of oropharyngeal or esophageal candidiasis. However, they are not frequently used for these latter indications due to their parenteral-only presentation [272–277].

Although echinocandins are not the choice to treat aspergillosis, they had shown useful for the treatment of refractory aspergillosis, when used in combination with voriconazole or with amphotericin lipid formulations [278–280]. Caspofungin has FDA approval as salvage therapy of invasive aspergillosis, and current IDSA guidelines stated that caspofungin or micafungin can be used to treat aspergillosis in settings in which azole and polyene antifungals are contraindicated [35]. There is also limited evidence supporting the use of echinocandins in combination therapy for the initial treatment of aspergillosis. Association of anidulafungin to voriconazole therapy had shown improved outcome in comparison to monotherapy, although without statistical significance [203, 232, 281].

Because their low urinary excretion rate, echinocandins are not considered for the treatment of UTIs. However, patients with fluconazole-resistant *Candida* spp. or with hepatic injury and fluconazole-sensitive *Candida* spp. have been successfully treated with caspofungin [282].

2.3.6 Adverse Events and Toxicity

Due to the target of echinocandins is absent in human cells, these drugs cause less toxicity. Mostly, echinocandins are well tolerated and their adverse events are mild and similar for all the three drugs currently in use. Serious adverse events requiring treatment discontinuation are fewer with these drugs than with other systemic antifungals. Most common adverse events are gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal pain, abdominal distention, and constipation), laboratory alterations (increment of aminotransferases and alkaline phosphatase and bilirubin, hypokalemia, among others) and general disorders and administration site conditions (pyrexia, edema peripheral, Infusion-related reaction, pain at the site of infusion). Table 2.5 summarizes the most frequent adverse reactions, with frequency of at least 5% in any of the groups under evaluation, reported in clinical trials testing echinocandins [283–285].

Asymptomatic elevation of liver enzymes, 5–13% for aminotransferases and 12% for alkaline phosphatase, is less frequent in patients treated with echinocandins in comparison with azoles and amphotericin B. Because hepatitis, hepatomegaly, hyperbilirubinemia, and hepatic failure have been rarely reported, monitoring of hepatic enzymes is recommended when using echinocandins [226, 283–285]. Renal adverse event reported with the use of echinocandins involved mild decrease of serum potassium, reported between 11 and 20% in clinical trials, without significant drug related toxicity observed [226, 283–285]. Occurrence of anemia, neutropenia, and thrombocytopenia have been reported between 6 and 15% in clinical trials, but again hematologic toxicity attributed to echinocandins is infrequent [226, 283–285].

Table 2.5 Adverse reactions^a in patients who received ECHINOCANDINS in clinical trials^b, incidence 5% or greater in any of the groups under evaluation

Adverse reactions ^c	Caspofungin (n = 1951)		Micafungin (n = 479)		Anidulafungin (n = 131 ^d)	
	n	%	n	%	n	%
With at least one adverse reaction	1665	85			130	99
Investigations	901	46	191	40	66	50
Alanine Aminotransferase Increased	258	13	45	10	7	5
Aspartate Aminotransferase Increased	233	12				
Blood Alkaline Phosphatase Increased	232	12			15	12
Blood Potassium Decreased	220	11			33	25
Blood Bilirubin Increased	117	6				
Urine output decreased			18	4		
White blood cell increased					11	8
Blood creatinine increased					7	5
Hypomagnesemia					15	12
Hypoglycemia					9	7
Hyperkalemia					8	6
Hyperglycemia					8	6
General disorders and administration site conditions	843	43	256	53	70	53
Pyrexia	381	20	103	22	23	18
Chills	192	10				
Edema Peripheral	110	6			14	11
Infusion-related reaction			24	5		
Chest pain					7	5
Gastrointestinal disorders	754	39	285	60	81	62
Diarrhea	273	14	106	22	24	18
Nausea	166	9	91	19	32	24
Vomiting	146	8	91	19	23	18
Abdominal Pain	112	6	76	16	8	6
Abdominal Distension			29	6		
Constipation					11	8
Blood and lymphatic system disorders			161	34	34	26
Thrombocytopenia			70	15	8	6
Neutropenia			61	13		
Anemia			63	13	12	9
Febrile neutropenia			23	5		
Leukocytosis					7	5
Infections and infestations	730	37			82	63
Pneumonia	115	6			8	6

(continued)

Table 2.5 (continued)

Adverse reactions ^c	Caspofungin (n = 1951)		Micafungin (n = 479)		Anidulafungin (n = 131 ^d)	
	n	%	n	%	n	%
Bacteremia					23	18
Urinary tract infection					19	15
Sepsis					9	7
Respiratory, thoracic, and mediastinal disorders	613	31	194	41	67	51
Dyspnea					15	12
Pleural effusion					13	10
Respiratory distress					8	6
Cough	111	6			9	7
Epistaxis			45	9		
Cardiac disorders			97	20		
Tachycardia			47	10		
Renal and urinary disorders			78	16		
Hematuria			18	4		
Psychiatric disorders			80	17	48	37
Anxiety			35	7		
Insomnia					20	15
Confusional state					10	8
Depression					8	6
Skin and subcutaneous tissue disorders	520	27	197	41		
Rash	159	8	55	12		
Erythema	98	5				
Pruritus			54	11		
Urticaria			24	5		
Decubitus ulcer					7	5
Nervous system disorders	412	21				
Headache	193	10			11	8
Vascular disorders	344	18			50	38
Hypotension	118	6			19	15
Hypertension					15	12
Deep vein thrombosis					13	10
Musculoskeletal and connective tissue disorders					27	21
Back pain					7	5

Source: References [283–285]

^aDefined as an adverse reaction, regardless of causality, while on echinocandins or during the 14-day post-echinocandins follow-up period^bIncidence among individuals who received at least 1 dose of trial drug^cWithin any system organ class, individuals may experience more than 1 adverse event^dPatients receiving 100 mg for the treatment of Candidemia/other Candida Infections

Infusion of echinocandins produces several histamine-release symptoms, including rash, pruritus, hypotension, bronchospasm, angioedema, and may be some acute cardiovascular events. Their occurrence is associated with the infusion rate and in most patients is enough to slow it to obtain improvement. In the case of anidulafungin, the infusion rate should not exceed 1.1 mg/min [226, 283–285]. In addition, rare cases of anaphylaxis, erythema multiforme, Stevens–Johnson syndrome, and skin exfoliation have been associated with the use of echinocandins, although a causal relationship has not been established [283–285].

2.3.7 Drug Interactions

Because echinocandins are not significant inhibitors or inducers of the CYP450 enzymatic pathways or p-glycoprotein drug efflux transporters, they have very few drug–drug interactions when compared with other systemic antifungals [226]. There are mild interactions of caspofungin with the immunosuppressant tacrolimus and cyclosporine. In the case of tacrolimus, standard drug monitoring of tacrolimus is recommended. The concomitant use of caspofungin with inducers of hepatic CYP enzymes is expected to reduce the plasma concentration of caspofungin. Then adult patients receiving rifampin, which is a potent inducer of CYP3A4, should receive 70 mg/day and pediatric patients 70 mg/m²/day of caspofungin. The same dosing should be considered when patients receive other inducers such as efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine [283].

There is no drug–drug interaction of micafungin with mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, fluconazole, and voriconazole.

In the case of nifedipine and itraconazole, the concomitant use of micafungin increment their AUC and C_{\max} , while sirolimus AUC was increased but its C_{\max} not. It is recommended that patients receiving micafungin with sirolimus, nifedipine or itraconazole should be monitored for these drugs, which dose should be reduced if necessary [284]. There is not drug–drug interaction of anidulafungin with cyclosporine, voriconazole, tacrolimus, rifampin, or amphotericin B liposomal [285].

2.3.8 Use in Special Population and Dose Adjustments

Pediatric Caspofungin and micafungin have FDA approval for use in children. Larger doses based on milligrams per kilogram are prescribed for both children and infants because the increased rate of clearance of these drugs among neonates, infants, and younger children compared with adolescents and adults [226, 286]. Caspofungin is considered safe and effective for pediatric patients older than 3 months, having the same indications as adults, with dosing based on body surface

area [283]. Micafungin is approved for pediatric patients older than 4 months and is dosed in mg/kg [284].

Pregnancy and Nursing Mothers All three echinocandins are class C agents in the pregnancy category. They should be used only if the potential benefit justifies the risk to the fetus. In animal studies, echinocandins caused embryofetal toxicity, including skeletal changes, increment of abortions and visceral abnormalities. Echinocandins could be detected in the plasma of the fetus, indicating they cross the placental barrier in rats. It is unknown if echinocandins are excreted in human breast milk, but they could be detected in the milk of lactating rats. Again, they should be administered to nursing mothers only if the potential benefit justifies the risk [226, 283–285].

Dose Adjustments As described above, a 70 mg/day dose of caspofungin is recommended when adult patients use rifampin concomitantly, while the pediatric dose is 70 mg/m²/day. The same dosing should be considered if there is concomitantly use of other inducer of CYP450, such as carbamazepine, dexamethasone, efavirenz, nevirapine, or phenytoin [283–285]. There is no need of dose adjustment in presence of renal insufficiency, including patients in hemodialysis or continuous renal replacement therapy [226, 283–285]. In the case of adults with mild hepatic insufficiency, maintenance dose of caspofungina is the same. This should be reduced to 35 mg/day in the case of moderate hepatic insufficiency (Child-Pugh score 7 to 9). There is no recommendation available for dosing caspofungin in adults with severe hepatic insufficiency or pediatric patients with any degree of hepatic insufficiency [283]. There is no need of dose adjustment of micafungin or anidulafungin in presence hepatic insufficiency of any degree [284, 285].

Obesity Because clearance of echinocandins increment with body weight and there is no difference in outcomes of obese and nonobese patients receiving the same dose of caspofungin, it is recommended an increment between 25 and 50% of the daily dose only for patients weighting 75 kg with severe infection [226, 287].

2.3.9 Adult Dosing

The dosing of echinocandins is slightly variable according with the indication. See Table 2.6.

2.3.10 New Echinocandin

Currently, a new echinocandin, named CD101/Bifungina, is under development for topical and weekly IV administration. It exhibits prolonged stability in plasma and aqueous solutions up to 40 °C [288], and has shown in vitro activity against resistant *Candida* spp. and *Aspergillus* spp. strains. There are two phase II studies currently enrolling patients.

Table 2.6 Dosing of echinocandins for adults by indication

Indication	Caspofungin	Micafungin	Anidulafungin
Esophageal candidiasis	Loading dose 70 mg IV, then 50 mg IV daily	150 mg IV daily; no loading dose is required	200 mg IV daily
Invasive candidiasis	Loading dose 70 mg IV, then 50 mg IV daily	100 mg IV daily; no loading dose is required	Loading dose 200 mg IV, then 100 mg IV
Salvage therapy for invasive aspergillosis*	Loading dose 70 mg IV, then 50 mg IV daily. Daily dose can be increased to 70 mg if response is inadequate	150 mg IV daily; no loading dose is required	Loading dose 200 mg IV, then 100 mg IV
Neutropenic fever (empiric therapy)	Loading dose 70 mg IV, then 50 mg IV daily		
Candida prophylaxis in hematopoietic cell transplant recipients		50 mg IV daily; no loading dose is required	

Source: References [283–285]

*Only caspofungin has US Food and Drug Administration approval for this indication

2.4 Flucytosine

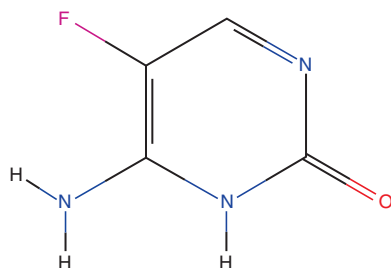
2.4.1 Chemical Structure

Flucytosine (5-fluorocytosine or 5-FC) is a synthetic nucleoside analogs chemically related to anticancer drugs (fluorouracil and floxuridine). Its molecular formula is C₄H₄FN₃O with a MW of 129.1 (Fig. 2.4).

2.4.2 Mechanism of Action

Flucytosine is transferred into fungal cells by cytosine permeases, where it is converted into 5-fluorouracil and phosphorylated to 5-fluorodeoxyuridine monophosphate. This compound inhibits thymidylate synthase, a crucial enzyme in the synthesis of 2'-deoxythymidine-5'-monophosphate that is an essential precursor for DNA biosynthesis, therefore disturbing DNA synthesis [290]. In addition, the 5-fluorodeoxyuridine monophosphate can be further phosphorylated and be incorporated to RNA, disrupting protein synthesis [291].

Fig. 2.4 Chemical structure of flucytosine.
Source: Reference [289]



2.4.3 Pharmacokinetics and Pharmacodynamics

A feature of the drug is its almost complete and fast absorption after oral administration, having a bioavailability of 76–89% [292]. The AUC is 62 mg·h/L and the maximal concentration is 80 µg/mL [290]. Flucytosine (5-FC) achieves fungistatic levels quickly and distributes extensively throughout the body fluids, including eyes and the cerebrospinal fluid, where it reaches approximately 75% of serum levels.

The 5-FC half-life in humans with normal kidney function is 3–5 h, but it is considerably delayed to 30–250 h in renal insufficiency [293, 294]. Only 2–4% of 5-FC is protein binding, between 80 and 90% is eliminated unchanged in the urine, and the liver metabolizes only a minimal amount. Flucytosine is removed by hemodialysis in 66–75%, but peritoneal dialysis is not as effective as hemodialysis [292, 295].

2.4.4 Spectrum of Activities and Resistance

Flucytosine is active against *C. neoformans* and *Candida* species except *C. krusei*, but isolates of *Aspergillus* species are usually nonsusceptible to 5-FC in vitro. Exist synergy with amphotericin B, which modifies the permeability of the fungal cell membrane allowing greater penetration of 5-FC.

Fungi with primary resistance to 5-FC are rare. A mutation in the *FCY2* gene, which encodes the cytosine permease, affects the absorption of the drug diminishing accumulation of the drug within the cell [296, 297]. Secondary resistance develops during therapy, especially during monotherapy, and it is based on inactivation of enzymes of the pyrimidine pathway. Mutations in the *FCY1* gene that encodes for the cytosine deaminase, or mutation in the *FURI* gene that encodes for the uracil phosphoribosyl transferase induce acquired resistance by interference in the conversion of 5-FC to 5-fluorouracil, or from 5-fluorouracil to 5-fluorouridine monophosphate respectively [296–300].

Other resistance mechanisms have been suggested for *C. glabrata*. It was found that in the presence of 5-FC the fungal cell wall showed higher resistance to lyticase, suggesting that cell wall alteration occurs in response to 5-FC. Genes CgFPS1 and CgFPS2 of *C. glabrata*, encoding a plasma membrane aquaglyceroporin, are

recognized as factors of 5-FC resistance. Both genes facilitate resistance by declining 5-FC accumulation in *C. glabrata* cells. Unlike, the deletion of CgFPS2 and particularly of CgFPS1 was found to improve the susceptibility to 5-FC registered for the parental strain [301].

2.4.5 Clinical Uses

Flucytosine should be used in combination therapy, generally with amphotericin B (Amph B), to decrease development of resistance. This combination is recommended as primary therapy for cryptococcal meningitis, severe pulmonary cryptococcosis and cryptococcemia [30]. Additionally, 5-FC in combination with Amph B is used for patients with refractory *Candida* infections, such as endocarditis, meningitis, or endophthalmitis and it is also recommended for the treatment of symptomatic ascending *Candida* pyelonephritis due to fluconazole-resistant *C. glabrata* [29].

The ESCMID and ECMM guidelines for the management of rare invasive yeast infections recommend amph B alone or in combination with 5-FC for infections due to *Geotrichum candidum* or *Rhodotorula* spp. They suggest the combination of amph B and 5-FC for infections due to *Saccharomyces cerevisiae*, and the combination of triazole plus echinocandin plus 5-FC to treat cerebral abscess due to dematiaceous fungi when surgery is not possible [30, 302].

2.4.6 Adverse Events and Toxicity

The toxicity to 5-FC is dose-dependent. The most frequent adverse events with this drug are bone marrow depression (leukopenia, anemia, and thrombocytopenia) and gastrointestinal disturbances (nausea, vomiting, diarrhea, abdominal pain, anorexia, dry mouth, and duodenal ulcer) [303–308]. Although bone marrow toxicity can occur with lower serum concentrations of 5-FC, it is more frequent when the concentration is greater than 100 µg/mL [305, 309]. For this reason, it is necessary to monitor the 5-FC serum concentrations to be sure they range between 25 and 100 µg/mL [310].

Less frequently, toxicity occurs in the central nervous system (headache, drowsiness, confusion, vertigo, and hallucinations) or manifest as liver function test abnormalities (jaundice, bilirubin elevation, increased hepatic enzymes, and acute hepatic injury). Colitis is reported infrequently, with toxicity related to local cytotoxic effect on protein synthesis [311–313].

Recently, a study performed in mice suggests that therapy with amph B combined with 5-FC originates a synergistic inflammatory activation in a dose-dependent way in hepatic tissues. Caution when using this antifungal combination is required, particularly for patients with hepatic deficiency [314].

2.4.7 Drug Interactions

Use of clozapine or deferiprone concurrently with 5-FC is not advised. They procainamide. Use of cytosine arabinoside could deactivate the antifungal action of 5-FC by competitive inhibition [290].

It was also noted that drugs which decrease glomerular filtration may extend the half-life of 5-FC [315]. Amph B-associated nephrotoxicity will delay elimination of 5-FC, causing an increase in serum 5-FC concentrations, may increase the risk and severity of bone marrow toxicity. Others agents that can increase the myelotoxic risk and therefore caution should be exercised in their use concomitantly with 5-FC are antineoplastic drugs (cyclophosphamide, doxorubicin, methotrexate, paclitaxel, vinblastine), antiviral agents (gancyclovir, foscarnet), antirretrovirals (zidovudine, lamivudine, didanosine, stavudine), chloramphenicol, dapsone, interferon alfa, linezolid, pentamidine and procainamide.

2.4.8 Use in Special Population

Dose adjustment is necessary in patients with renal dysfunction. In that case, the dose interval has to be extended (see Table 2.7). With a creatinine clearance below 10 mL/min, 5-FC serum levels should be monitored, doing appropriate dose adjustments so not to exceed 80 µg/mL. Because 5-FC is dialyzable, the daily dose must be administered post hemodialysis.

Because of reduced renal function in neonates with a very low birth weight, use of 5-FC in this population should be done with very close monitoring of serum drug levels to avoid large accumulation of 5-FC in plasma [72]. Flucytosine is considered as category C according to the FDA pregnancy category (animal studies show toxicity, human studies inadequate but benefit of use may exceed risk). It is contraindicated during early pregnancy (first trimester) because the drug crosses the human placenta and for its known teratogenic effect in rats and its interference with DNA synthesis in the growing fetus [320, 321]. The delivery of 5-FC in human milk is unknown, and its use during breastfeeding is not recommended. Dosing of 5-FC in obese patients is that for the ideal body weight.

Table 2.7 Flucytosine dosing in adult people according to glomerular filtration rate (standard dose of 100–150 mg/kg/day)

Renal clearance mL/min	Dose	Period (h)
>50	25–37.5 mg/kg	Every 6 h
10–50	25–37.5 mg/kg	Every 12–24 h
<10	25–37.5 mg/kg	Every 24–48 h
Hemodialysis	25–50 mg/kg	Dose post-dialysis, every 48–72 h
Peritoneal dialysis	0.5–1.0 g	Every 24 h

Source: Data from [316–319]

2.5 Terbinafine

Terbinafine is a drug that belongs to the allylamine group, which includes also the topical antimycotic naftifine. Terbinafine is potent inhibitors of ergosterol biosynthesis, available as tablets, spray, cream, and gel formulations.

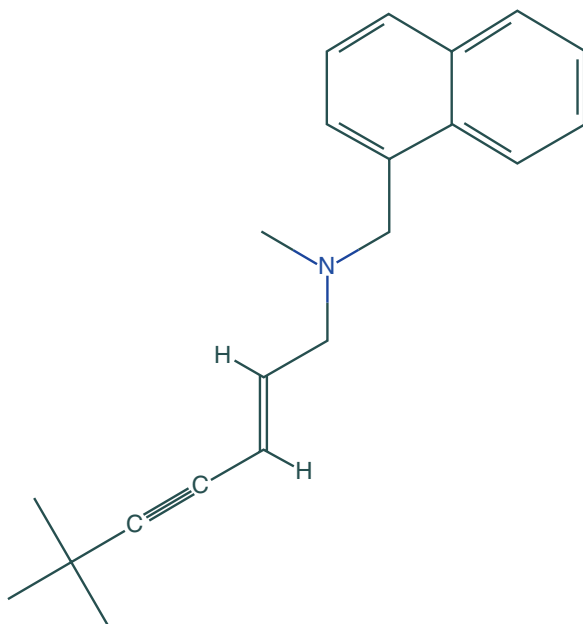
2.5.1 Chemical Structure

Chemically, terbinafine is (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine hydrochloride with a MW of 327.90 (Fig. 2.5).

2.5.2 Mechanism of Action

Terbinafine acts as antifungal drug by noncompetitive inhibition of squalene epoxidase, an enzyme that converts the squalene into 2,3-oxidosqualene that then form lanosterol, which is a precursor of ergosterol, an essential constituent of fungal membrane. At that point, the intracellular accumulation of squalene, which is toxic to fungal cells, and a deficiency in ergosterol cause a quick cell death [323, 324].

Fig. 2.5 Chemical structure of terbinafine.
Source: Reference [322]



2.5.3 *Pharmacokinetics and Pharmacodynamics*

Terbinafine is well absorbed from the gastrointestinal tract, with a bioavailability ranging from 70 to 85%, which varies discretely when it is taken with foods no requiring dose modification. It has a low affinity for muscle, spleen, and brain tissues, but it has high affinity for the skin and adipose tissues, which are the largest depot for the antifungal drug [325, 326].

Gastric acidity does not seem to influence the absorption. Terbinafine reaches maximal plasma concentrations approximately 2 h after a single dose, getting high concentrations in the adipose tissue, stratum corneum, dermis, epidermis, sebum, nails, and in the hair follicle [327–329]. Penetration of the antifungal drug into the brain ranges between 6 and 43% of the plasma concentration, and is undetectable in CSF [325].

Linear dose-proportional pharmacokinetic has been proven after a range of single doses from 125 to 750 mg of terbinafine [330]. Steady-state plasma levels of terbinafine are attained after 10–14 days of treatment decreasing rapidly after the end of treatment [331, 332]. Plasma half-life ranges from 16 to 26 h after administration of 250 mg of terbinafine in healthy volunteers. A supplementary elimination phase with a half-life of more than 90 h was detected after administration of radiolabelled terbinafine [333–336].

This antifungal drug is extremely lipophilic, 99% protein bound and it has a good penetration in the keratinized tissue, reaching active concentrations in nail in 1–2 weeks. A characteristic of this drug is to remain in the nail in therapeutic concentrations for a long time after discontinuing the drug. Terbinafine is not detected in sweat [328, 329, 335].

Terbinafine is metabolized by the liver. Several cytochrome isoenzymes are involved in the main pathways of terbinafine metabolism. Some of them are CYP2C9, CYP2C8 and CYP1A2 (N-demethylation), CYP3A4 (deamination), CYP2C9, CYP2C8, CYP2C19, and CYP1A2 (alkyl side chain oxidation) and, CYP2C9 and CYP1A2 (dihydrodiol formation). The multiple cytochrome P-450 s implicated in the metabolism of this drug indicates a reduced potential for drug–drug interactions [337, 338]. Nonetheless, terbinafine may inhibit the metabolism of CYP2D6 substrates. It could be important for the interaction with some drugs that are known substrates of CYP2D6 such as amitriptyline, carvedilol, codeine, haloperidol, metoprolol, paroxetine, risperidone, and tramadol. The coadministration of terbinafine with these drugs with could cause a prolonged increase in their plasma levels [339].

Terbinafine is excreted mainly in the urine (80%) and in small amounts in feces (20%) [335]. In children, a dosage adjustment according to bodyweight is recommended because AUC values are significantly higher than in young adults [340].

2.5.4 Spectrum of Activities and Resistance

Terbinafine has potent antifungal activity against a diversity of dermatophytes isolated from patients worldwide, including *Trichophyton tonsurans*, *Microsporum canis*, *M. gypseum*, *T. verrucosum*, *T. violaceum*, *M. audouinii*, *T. rubrum*, *T. interdigitale*, *T. mentagrophytes*, and *Epidermophyton floccosum* [341–343]. Also, in vitro studies have shown that terbinafine is highly active against *Sporothrix brasiliensis*, *S. schenckii*, and *S. globosa* isolated from clinical samples in Brazil [344, 345], and for a wide variety of agents of chromoblastomycosis [346]. Terbinafine is only moderately active against *Madurella mycetomatis* isolates [347].

2.5.5 Clinical Uses

Terbinafine is available in different formulations, tablets, and topical preparations such as cream, jelly, spray, and solution. Topical formulations are used to treat superficial fungal infections due to dermatophytes or *Candida* species.

Terbinafine is the first line treatment for toenail onychomycosis due to dermatophytes [348, 349]. This antifungal drug presents the greatest rate of mycological cure according to results from a systematic review and a network meta-analysis conducted to compare the relative efficacy of treatments for onychomycosis due to dermatophyte [350]. Oral terbinafine has been also proved effective in treating onychomycosis due to *Scopulariopsis* species [350–352].

Terbinafine is also indicated for tinea capitis caused by *Trichophyton* species in children. A meta-analysis of randomized, controlled trials comparing griseofulvin and terbinafine for the treatment of tinea capitis has shown that terbinafine is superior for tinea capitis caused by *Trichophyton* spp., whereas griseofulvin is superior when *Microsporum* spp. is the etiological agent [353, 354]. For other tinea infections (corporis, cruris, or pedis) without response with cream/gel, oral terbinafine may be used.

For cutaneous and lymphocutaneous sporotrichosis, terbinafine administered at a dosage of 500 mg orally twice daily is considered a safe alternative treatment (A-II) to itraconazole [142]. Based in reports showing successful outcome using combination therapy including terbinafine for treating *Scedosporium* infections, the ESCMID and ECMM joint guidelines proposes the use of caspofungin plus terbinafine as salvage therapy for *Scedosporium* spp. infections in cystic fibrosis patients with lung transplantation (quality of evidence and strength of recommendation: CIII) and voriconazole plus terbinafine for patients with lung infections, osteomyelitis/septic arthritis and for disseminated infection due to *S. prolificans* (quality of evidence and strength of recommendation: BIII) [355–359].

ESCMID also recommends use of an azole or terbinafine plus surgery (AIII) for the treatment of eumycetoma or combination therapy with azoles plus terbinafine or flucytosine for refractory eumycetoma cases (B III). High-dose of terbinafine (1000 mg/day) alone for 24–48 weeks had shown to be clinically effective and well tolerated when used to treat patients with eumycetoma, whose only therapeutic option is surgery. Among 23 eumycetoma patients, 16 out of 20 who completed the study showed improvement or cure [360].

Few case reports about successful outcome of the use of terbinafine plus amphotericin B in the treatment of disseminated fusariosis had been published [361, 362].

Terbinafine can be used as alternative to itraconazole (BIII) in the treatment of chromoblastomycosis, and in combination with itraconazole for cases of refractory disease [302]. Terbinafine dosing for the most common indications in adult and pediatric patients are shown in Tables 2.8 and 2.9.

2.5.6 Adverse Events and Toxicity

Terbinafine is an antifungal drug well tolerated even in people over 65 years, many of whom may be taking antihypertensives, antidiabetics, or lipid-lowering agents concomitantly [363]. Adverse reactions related to terbinafine are usually mild in

Table 2.8 Terbinafine dosing for the most common indications in adult patients

Fungal disease	Doses (mg)	Duration	Comments
Tineas corporis or cruris	250 qd	2–4 weeks	
Tinea pedis	250 qd	2–6 weeks	
Tinea capitis	250 qd	6 weeks	Dosing for patients with more than 40 kg
Onychomycosis	250 qd	6 weeks (fingernails) or 12 weeks (toenails)	Sometimes a treatment for >6 months may be necessary
Sporotrichosis	500 bid	Until 2–4 weeks after clinical cure	Usually for 3–6 months

Source: References [142, 332, 348–350, 363]

Table 2.9 Pediatric dosing according body weight in patients with onychomycosis

Body weight (kg)	Doses (mg)	Comments
10–20	62.5	6 weeks (fingernails) or 12 weeks (toenails)
20–40	125	6 weeks (fingernails) or 12 weeks (toenails)
>40	250	6 weeks (fingernails) or 12 weeks (toenails)

Source: Reference [348]

severity. Gastrointestinal complaints are common events [364]. Patients on treatment with this drug may complain of nausea, diarrhea, bloating, dyspepsia, epigastric pain, and other less-frequent gastrointestinal symptoms [365]. More rare effects are skin reactions, cholestatic hepatitis and taste loss [366–369]. The frequency of taste loss ranges between 0.1 and 1% [369]. Risk factors associated with taste loss due to terbinafine are age (65 years and older, OR: 4.4, 95% CI: 1.4–16.1) and body mass index below 21 kg m² (OR:4.4, 95% CI: 1.6–14.2). The OR of taste loss in patients 55 years and older with a BMI below 21 kg m² is 12.8 when comparing with patients below 35 years old (95% CI: 1.9–88.6) [370].

Cutaneous adverse effects of terbinafine have a wide spectrum of presentation and are infrequent, having been reported in less than 2% of the patients. Recently, a case report of terbinafine-induced lichenoid drug eruption in a patient receiving the antifungal drug for 2 weeks was published. Lesions disappeared totally after 8 weeks of drug withdrawal [371]. Other rare cutaneous side effect induced by terbinafine is pityriasis rosea [372]. Also, the induction of subacute cutaneous lupus erythematosus and exacerbation of systemic lupus erythematosus by terbinafine have been reported [373, 374].

The incidence of serious side effect is less than 1%. Cases of Stevens-Johnson syndrome, neutropenia/agranulocytosis, thrombocytopenia, and aplastic anemia have been rarely reported [375–384]. Hepatotoxicity (including acute hepatitis, cholestasis, acute liver failure and vanishing bile duct syndrome) due to terbinafine has an incidence of 0.5–3/100,000. In most of these events improve after discontinuation of the drug [385–387]. A mixed hepatitis-cholestatic liver injury has also been reported [388].

2.5.7 Drug Interactions

Terbinafine does not inhibit or induce CYP 3A4, but it inhibits CYP2D6. Then, interactions with drugs that are metabolized by CYP 2D6 such as tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, doxepin, imipramine, nortriptyline), β -blockers (atenolol, metoprolol, propranolol, timolol, carvedilol), type B monoamine oxidase inhibitors (rasagiline and selegiline), some antipsychotic (chlorpromazine, haloperidol, risperidone, thioridazine), certain arrhythmics (lidocaine, procainamide), several medications for attention deficit hyperactivity disorder (atomoxetine, methamphetamine, methylphenidate), chloroquine, mirtazapine and dextromethorphan can potentially occur, increasing risk of side effects of these drugs. Concomitant use of tamoxifen with terbinafine should be avoided because it causes a decrease of endoxifen, one of the most important metabolites of tamoxifen, thereby decreasing the effectiveness of tamoxifen [389]. Terbinafine also mildly inhibits the metabolism of cyclosporine with little clinical significance [390].

2.5.8 Use in Special Population

No dosage modification is necessary in elderly patients. Terbinafine is contraindicated for patients with chronic or active hepatic disease [391]. Also, it is not recommended for patients with creatinine clearance lower than 50 mL/min because there are not satisfactory studies to confirm its safety in this population. Terbinafine has not been associated with any teratogenic toxicity in animals. Although it is not known whether terbinafine crosses the human placenta, it is categorized as a Pregnancy Category B drug by the FDA. The product labeling recommends against its use during pregnancy for both, topical and oral formulations. Small amounts of terbinafine are excreted in breast milk contraindicating its use in breastfeeding mothers [392].

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