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REVIEW

Sixty years of Amphotericin B: An Overview of the Main Antifungal Agent Used to Treat Invasive Fungal Infections

Francelise B. Cavassin · João Luiz Baú-Carneiro · Rogério R. Vilas-Boas · Flávio Queiroz-Telles

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ABSTRACT

Introduced in the late 1950s, polyenes represent the oldest family of antifungal drugs. The discovery of amphotericin B and its therapeutic uses is considered one of the most important scientific milestones of the twentieth century . Despite its toxic potential, it remains useful in the treatment of invasive fungal diseases owing to its broad spectrum of activity, low resistance rate, and excellent clinical and pharmacological action. The well-reported and defined toxicity of the conventional drug has meant that much attention has been paid to the development of new products that could minimize this effect. As a result, lipid-based formulations of amphotericin B have emerged and, even keeping the active principle in common, present distinct characteristics that may influence therapeutic results. This study presents an overview of the pharmacological properties of the different formulations for systemic use of amphotericin B available for the treatment of invasive fungal infections, highlighting the characteristics related to their chemical, pharmacokinetic structures, drug–target interactions, stability, and others, and points out the most relevant aspects for clinical practice.

Keywords: Fungal disease; Lipid formulation; Polyenes; Safety; Tolerability

F. B. Cavassin (✉)
Clinical Medicine Department, Federal University of Paraná (UFPR), Curitiba, PR, Brazil
e-mail: fran_cavassin@yahoo.com.br

F. B. Cavassin
Faculty of Medical Sciences, Faculdades Pequeno Príncipe (FPP), Curitiba, PR, Brazil

J. L. Baú-Carneiro
Medical School Undergraduate Program, Faculdades Pequeno Príncipe (FPP), Curitiba, PR, Brazil

R. R. Vilas-Boas
Faculty of Pharmacy and Biomedical Sciences, Faculdades Pequeno Príncipe (FPP), Curitiba, PR, Brazil

F. Queiroz-Telles
Department of Public Health, Hospital de Clínicas, Federal University of Paraná (HC-UFPR), Curitiba, PR, Brazil

Key Summary Points

Amphotericin B (AMB) is still considered one of the most important antifungals of the last 60 years.

We present an overview of the pharmacological properties of the different formulations for systemic use of AMB available for the treatment of invasive fungal infections.

The study highlights its chemical characteristics, pharmacokinetic, structures, drug–target interactions, stability, bioequivalence, and others, and points out the most relevant aspects for clinical practice.

The indications for the different formulations of AMB are based on the latest consensus and guidelines, and studies on their toxicity are based on the main clinical trials conducted in humans.

A timeline presents the main scientific milestones for AMB over the decades.

An updated list of the last 2 years of clinical trials that seek to improve the use of AMB in different situations is also provided.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13325681.

INTRODUCTION

Licensed in 1959 [1], amphotericin B (AMB) was initially designed for the treatment of local mycotic infections and later approved for the treatment of progressive and potentially fatal fungal infections [2]. After 60 years, it is still an important option in the treatment of fungal diseases.

Traditionally, the drug is administered as a formulation of deoxycholate amphotericin B (D-AMB) capable of forming micelles in aqueous solution [3]. Besides being a long-known medication, AMB has important side effects, such as nephrotoxicity, which have limited its indiscriminate use [4–6]. Most of the time, patients who need intervention with D-AMB are severely compromised because of their underlying diseases and comorbidities, and therefore, they end up becoming vulnerable to the reported toxic effects, especially when combined with other drugs.

To overcome this impasse, new systemic therapeutic options have been proposed: amphotericin B lipid complex (ABLC) and liposomal amphotericin B (L-AMB). There was a third lipid formulation known as AMB colloidal dispersion (ABCD), presented as uniform disk-shaped particles, that was discontinued in 2011 because of its high rate of infusion-related events and it is no longer manufactured [7, 8]. Although ABLC and L-AMB have the same active principle in common, their pharmacological characteristics distinguish them and may influence the final therapeutic results. Their chemical structures, pharmacokinetics, drug–target interactions, stability, bio and therapeutic equivalences share similarities but also present peculiarities, notably when compared to the conventional formulation.

This study presents an overview of the pharmacological and biopharmaceutical properties of the different systemic formulations of AMB available for the treatment of invasive fungal infections and highlights the most relevant aspects in 60 years for clinical practice. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

WHY THE GOLD STANDARD?

Amphotericin B is a life-saving drug in the treatment of serious systemic fungal infections

and is still the most widely used antifungal in and intensive care, despite the development of a series of new antifungal agents, especially the second-generation triazoles and the echinocandins.

These 60 years of clinical experience have proven that AMB is a reliable antifungal agent. At the time of its introduction and for decades, doctors had few other therapeutic options, and they learned and adapted to use it in order to minimize its toxicities.

The new therapeutic options also offer great prospects for treatment. Such options include improved azole antifungal agents, the echinocandin class, in addition to constant studies in search of new lipid formulations of AMB itself. However, it has been in recent years that these agents have proven their worth in a variety of clinical settings, providing high rates of effectiveness with minimal safety-related problems. Therefore, over time, it is natural that the use of conventional AMBs and even lipid formulations of amphotericin B (LFABs) may have limited use, as the evidence with the new agents, with new combination schemes, will show improvements in patient care and its benefits will be increasingly noticed.

Despite these advances, AMB remains in use both in medical practice and in clinical trials owing to the wide possibility of licensed indications. In addition, AMB remains the treatment of choice for many serious fungal infections in vulnerable hosts owing to its excellent spectrum of activity and its low resistance rates. To date, it continues to be the agent with the widest spectrum of action and the lowest resistance potential of any known antifungal agent [9].

Some characteristics that maintain its status as the gold standard are the low cost of conventional AMB therapy, the high acceptance of this formulation in continuous use by neonates, the improvement of toxicity rates with the arrival of the LFABs, and its intrathecal use in *Coccidioides immitis* meningitis [10, 11]. It is also noteworthy that there are individuals who actually tolerate conventional therapy better than advanced formulations [12]. Basically, these are the fundamentals that make the medical community consider the use of AMB as a therapeutic standard in addition to a standard comparator for clinical trials among antifungal agents.

With the new pharmaceutical forms and formulations, such as the possibility of the long-awaited AMB for oral use and the production of a generic version, for example, the cost of LFABs may start to decrease and its wide access will be offset by reduced rates of toxicity.

Finally, the newest treatment guidelines still mention its use as first-line therapy in certain defined situations, which reinforces AMB as the official holder of the gold standard title in the treatment of serious invasive fungal diseases.

HISTORICAL FINDINGS, CHARACTERISTICS, AND STRUCTURES

Amphotericin B belongs to the class of polyene macrolides which also comprises amphotericin A and nystatin, the latter being considered the first antifungal agent developed for the treatment of mycoses [13], despite its production as a systemic agent being avoided because of serious toxicities.

The drug was discovered in 1956 by Donovick, Gold, Pagano, and Stout [14] following the fermentation of the actinomycete *Streptomyces nodosus*, originally identified as M-4575, isolated from a soil sample collected in the Orinoco River region, in Venezuela. As a therapeutic agent, it was licensed in 1959, on the basis of available and non-comparative data [1], and became accessible commercially in 1960 as Fungizone® (Bristol-Myers-Squibb, USA), a colloidal suspension of AMB.

Currently AMB is certified for the treatment of various fungal and potentially fatal infections such as opportunistic mycoses, e.g., aspergillosis, candidiasis, cryptococcosis, fusariosis, mucormycosis, hyalohyphomycosis, and phaohyphomycosis, as well as severe and widespread forms of endemic mycoses, e.g., histoplasmosis, paracoccidioidomycosis, blastomycosis, coccidioidomycosis, sporotrichosis, talaromycosis (*Talaromyces marneffei*, formally *Penicillium marneffei*), and emergomycosis [15–19]. Lipotrophic molecules such as deoxycholate,

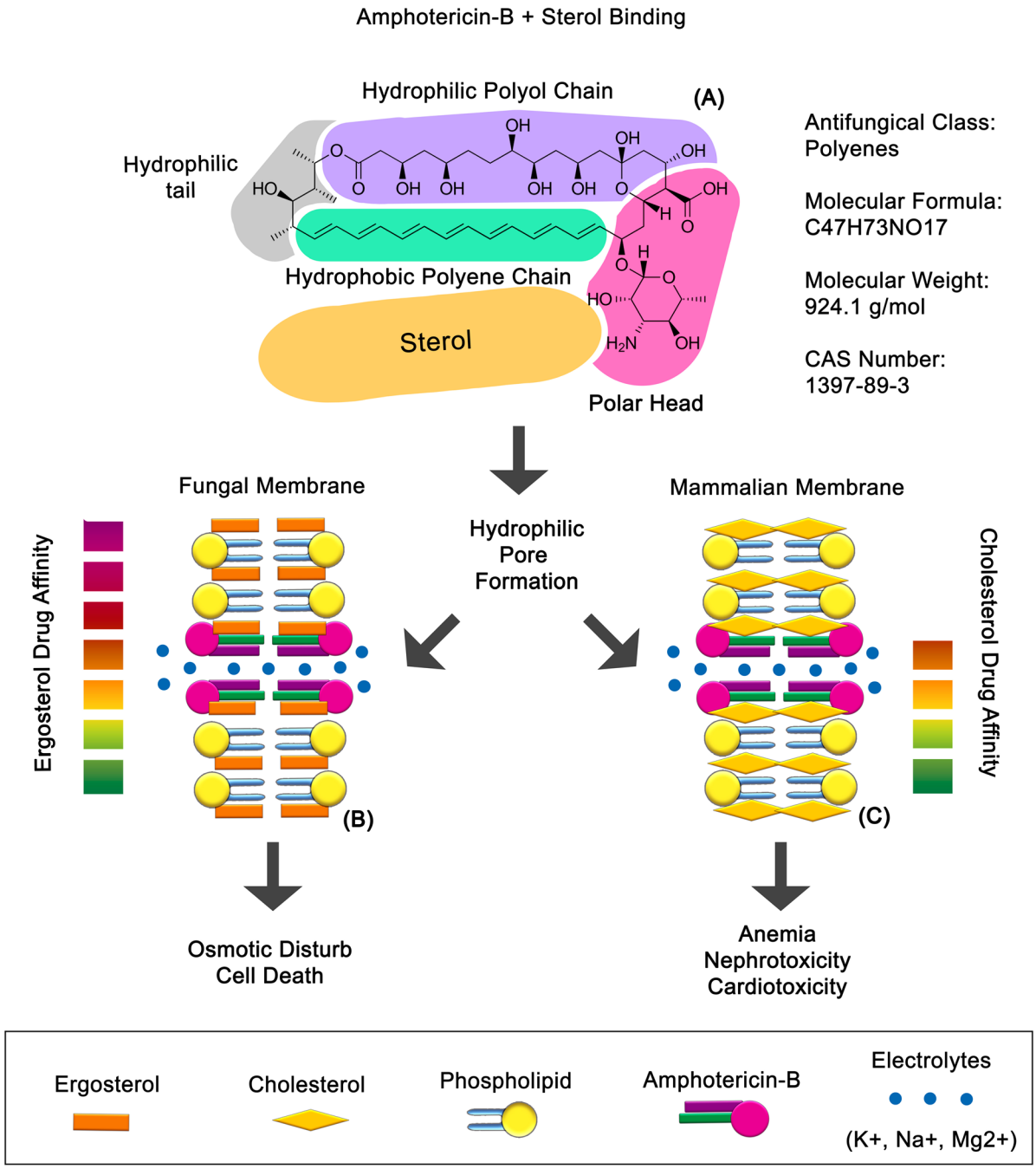

Fig. 1 **a** Drug summary and 2D chemical structure of AMB and its binding to the cell's sterol component; **b** AMB mechanism of action in a fungal cell; **c** AMB mechanism of toxicity in a mammalian cell

liposomes, and lipid complexes were added in the intravenous formulations for systemic use because of the insolubility of the standard form.

AMB comprises a 38-membered macrocyclic ring formed by lactonization and it has a chain of unsubstituted conjugated double bonds (heptaene) (Fig. 1a). On the opposite side, a polyhydroxylated chain with seven free hydroxyl groups guarantees it an amphipathic characteristic. A mycosamine residue (lactone) rests

at one end of the molecule, with a free amino group, forming a side chain [20]. The conventional formulation contains approximately 41 mg of sodium deoxycholate and 20.2 mg of phosphate buffer [21]. Sodium deoxycholate increases the solubility of amphotericin B in water, because, although AMB has an amphiphilic region, its solubility in water is low. Sodium deoxycholate also stabilizes the micellar suspension formed [22, 23]. The hydrophobic part of the molecule binds to ergosterol, the main sterol in the cytoplasmic membrane of fungi. As a result of this connection, pores and channels are formed in the plasma membrane that allow the extravasation of electrolytes from the intracellular medium such as potassium, ammonium, and phosphate in addition to carbohydrates and proteins, thus causing cell death [24–28].

This mechanism of action (Fig. 1b), added to an induction of oxidative damage in the fungal cell [28], guarantees its fungicidal characteristic. Nevertheless, the success of this interaction depends on the concentration of the drug in body fluids and on the fungal specimen's susceptibility to it.

Besides its affinity for the fungal ergosterol, AMB also stands out as a molecule with affinity for cholesterol present in mammalian cells (Fig. 1c). This characteristic per se explains why kidneys, heart, and blood cells are damaged during some therapeutic schemes [25, 29]. Despite that, there is no other antifungal medication that combines so many positive characteristics. Its potent fungicidal activity, broad spectrum of action, and rare induction of resistance guarantees it as an extremely effective option among other chemotherapeutic possibilities [30]. Studies have been conducted to improve lipid preparations as vehicles for new formulations such as liposomes [31–37], lipid complexes [38–40], emulsions [41–46], nanoparticles with dimercaptosuccinic acid [47], cationic lipid–polymer hybrids targeting macrophages [48], and Pluronic F127 micelles [49]. Figure 2 illustrates the main historical events of the last 60 years, maintaining AMB as the gold standard for the treatment of most invasive fungal infections (IFIs).

The current lipid formulations of amphotericin B (LFABs) available for clinical use differ in pharmacological characteristics such as structure, shape, size, composition, and toxicity—when compared to the conventional formulation (Table 1). ABLC and L-AMB allow the administration of higher doses and vary in efficacy and toxicity depending on the preparation and the species of fungus. Both benefits were goals for the development of LFABs, and the approval of these formulations was based on their comparison with conventional amphotericin B in clinical trials that are also cited in Table 1 for any further reading.

Although licensing decisions in the USA for LFABs have been based primarily on data from open non-comparative studies, there is now more available data that supports the effectiveness and safety of these compounds in the treatment of systemic fungal infections. The use of higher concentrations of AMB in less toxic lipid formulations is of great importance owing to its high clinical tolerability. However, undesirable effects such as fever, chills, stiffness, drowsiness, slight elevation in liver function tests, renal dysfunction, and cardiopulmonary toxicity have been documented even in patients who received those liposomal subtypes [58]; therefore, studies are still being carried out to find ways to reduce these events further. Recent research presented results regarding the development of nanoparticles, signaling superiority of these compounds to the conventional preparations [46–48, 60].

Infusion-related toxicity is a side effect which was initially attributed to the conventional formulation, as a result of the pro-inflammatory response to cytokines that manifests during the first minutes of administration. The symptoms are well controlled with antihistamines, analgesics, and corticosteroids [106].

It was the study by Gigliotti et al. [107] that postulated the chills and fever produced by an infusion of AMB were mediated through prostaglandin E_2 synthesis. After this understanding new findings started bringing attention to the use of premedication as new way to better prevent these side effects. Some trials—even decades before that—revealed that hydrocortisone could be effective in the prevention of infusion-related reactions because of its

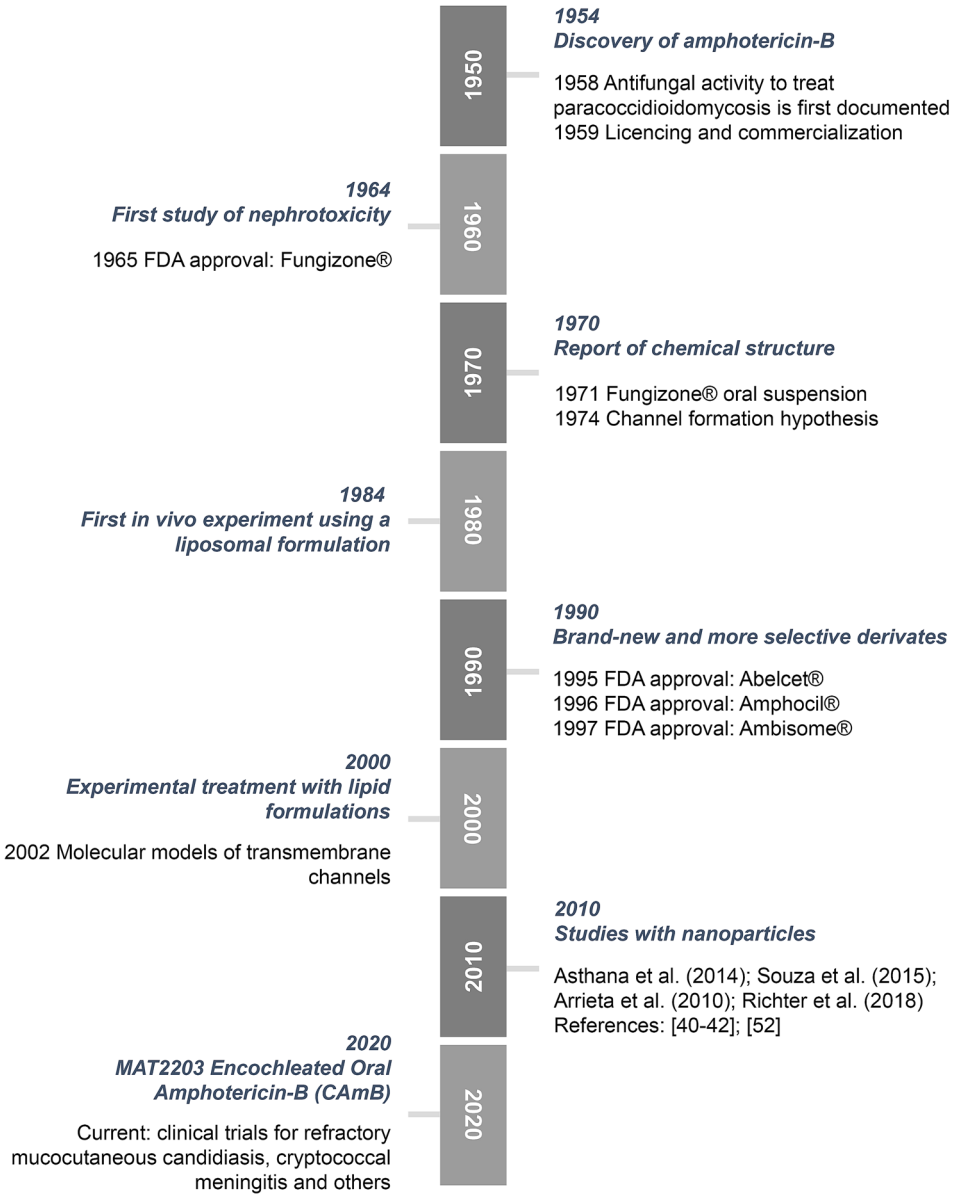

Fig. 2 Amphotericin B over the decades

cytokine transcription inhibitory property [108]. There are also studies about the use of opioids (mainly represented by meperidine IV in bolus) as a good option in ameliorating the infusion reactions. Authors argue that meperidine can eliminate these reactions more effectively and more rapidly than simply discontinuing the AMB [109]. Acetaminophen and metamizole are also commonly reported as drugs used for premedication.

In short, reactions related to the infusion of conventional therapy are possibly treatable. For patients who develop undesirable reactions, switching to an LFAB can also be a solution.

However, in 2003, Roden et al. [110] stated that the infusion of L-AMB could result in an idiosyncratic reaction manifested as a triad of chest pain and/or discomfort, flank and/or abdominal pain and dyspnea. This reaction is credited more to the liposome than the active drug itself [111], although Wade et at. [112]

Table 1 Pharmacological characteristics of and other general information on lipid-based formulations of amphotericin B (LFABs) available for systemic use and conventional formulation

Formulation	LFABs		Conventional
	ABLC	L-AMB	D-AMB
Reference	Abelcet®	AmBisome®	Fungizone®
Pharmaceutical industry	The Liposome Company Inc., NJ	Fujisawa Healthcare Inc., IL	Apothecon Products, Princeton Inc., NJ
FDA approval	1995	1997	1965
Structure	Multilamellar ribbon-shaped complex	Small spherical unilamellar liposomes	Micellar structure
Design	Fig. 3	Fig. 4	Fig. 5
Size (nm)	1600–11,000	< 100	< 25
Composition	AMB suspension complex with DMPC and DMPG	AMB encapsulated in liposomes consisting of hydrogenated soy phosphatidylcholine, cholesterol, and DMPG	Colloidal dispersion of AMB with deoxycholate salt in aqueous glucose solution
AMB content	100 mg in 20 mL of isotonic suspension	50 mg lyophilized powder	50 mg lyophilized powder
Standard dosage (mg/kg)	1.0–5.0	3.0–5.0	0.25–1.0
LD50 (mg/kg)	40	175	2
Distribution	Spleen ≫ liver = lung > kidney	Spleen ≫ liver > lung = kidney	Liver > spleen > lung > kidney
BBB overpass [50]	Partial	Yes	Yes
Indications* (Grade A or B of evidence) [15–17, 19, 51]	Yeast fungi: *Pseudozyma* spp., *Trichosporon* spp., *Candida* spp. Filamentous fungi: *Fusarium* spp., black fungi/ phaeohyphomycetes/ dematiaceous fungi Endemic infections: coccidioidomycosis, emergomycosis, paracoccidioidomycosis Invasive fungal infections in patient's refractory or intolerant to conventional therapy (D-AMB) or when L-AMB is not available	Yeast fungi: *Geotrichum* spp., *Kodamaea* spp., *Malassezia* spp., *Pseudozyma* spp., *Rhodotorula* spp., *Saccharomyces* spp., *Saprochaete* spp., *Sporobolomyces* spp., *Trichosporon* spp., *Candida* spp. Filamentous fungi: *Fusarium* spp., phaeohyphomycetes/dematiaceous fungi/black fungi, *Schizophyllum* and other basidiomycetes, *Scopulariopsis* spp., *Penicillium* spp., Paecilomyces Endemic infections: blastomycosis, coccidioidomycosis, emergomycosis, histoplasmosis, sporotrichosis, talaromycosis (penicilliosis) Empirical therapy for suspected fungal infection in patients with febrile neutropenia	Yeast fungi: *Geotrichum* spp., *Kodamaea ohmeri*, *Malassezia* spp., *Rhodotorula* spp., *Saccharomyces* spp.,*Trichosporon* spp., *Candida* spp. Filamentous fungi: – Endemic infections: blastomycosis, coccidioidomycosis, emergomycosis, histoplasmosis, paracoccidioidomycosis, sporotrichosis, talaromycosis (penicilliosis)

Table 1 continued

Formulation	LFABs		Conventional
	ABLC	L-AMB	D-AMB
Main studies** about therapeutical efficacy on IFI	[52–59]	[57, 60–71]	[62, 72–77]
Main studies** about toxicity	Renal	[53, 56, 57, 78–81]	
	Cardiac***	[82–93]	
	Hematological	[55, 78, 94]	
	Infusion-related	[53, 55, 57, 95–98]	
Comparative studies between different AMB formulations		[24, 79, 98–105]	

LFABs lipid-based formulations of amphotericin B, *ABLC* amphotericin B lipid complex, *L-AMB* liposomal amphotericin B, *D-AMB* amphotericin B deoxycholate, *DMPC* dimyristoylphosphatidylcholine, *DMPG* dimyristoylphosphatidylglycerol, *AMB* amphotericin B, *IFI* invasive fungal infection, *FDA* Food and Drug Administration, *BBB* blood–brain barrier, *LD50* median lethal dose

*Based on the most recent consensus

**Human clinical trials only

***Case reports described in the literature

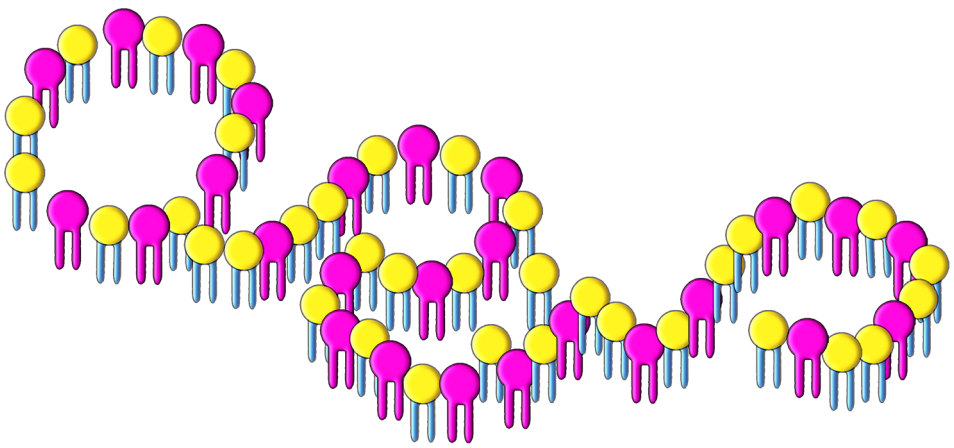

Fig. 3 Amphotericin B lipid complex (ABLC). Amphotericin B Phospholipid

ensured that the toxicity related to the infusion of L-AMB is consistently less that other formulations of polyenes, including ABLC.

For the lipid complex of AMB there are recommendation in case of adverse events, including the infusion-related ones. The document suggests as optimal premedication the use of hydrocortisone and chlorphenamine (antihistamine agent) given 15–30 min before the infusion. Other advice includes the minimum infusion time of 2 h and adequate hydration before and after dosing for renal function improvement [113].

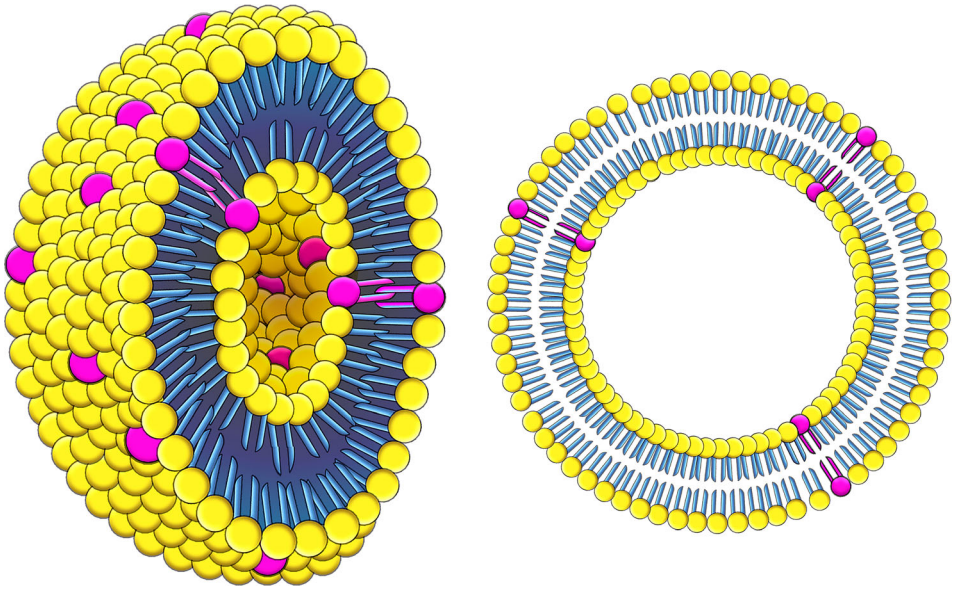

Fig. 4 Liposomal amphotericin B (L-AMB). Amphotericin B Phospholipid

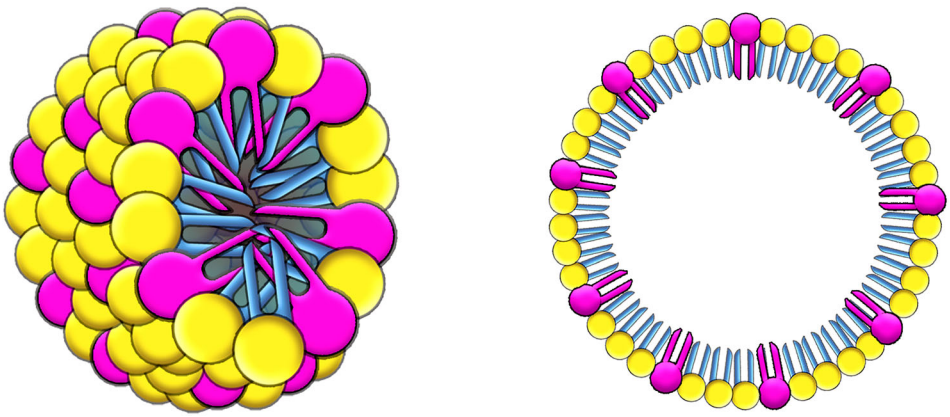

Fig. 5 Amphotericin B deoxycholate (D-AMB). Amphotericin B Phospholipid

PHARMACOKINETICS AND PHARMACODYNAMICS PROPERTIES

The understanding of the pharmacokinetic (PK) and pharmacodynamic (PD) properties of an antimicrobial agent is based on the exposure–response relationship between the drug and the pathogen. Such affinity can be established by integrating PK and PD parameters, such as both maximum concentration (C_{max}) and the area under the curve (AUC), and the minimum inhibitory concentration (MIC), respectively. As a result, optimal drug regimens are achieved, and toxicity and resistance development are minimized [114, 115].

To determine the PK/PD index of an antifungal, in vitro and in vivo studies are performed. In vitro susceptibility tests are needed to determine MIC in reproducible conditions and PK studies to estimate population

parameters (clearance and volume of distribution). At the end, there is a dose–response experiment to relate exposure to the antifungal effect using the drug fractionation [116]. For AMB, it is known that the PK/PD indices were previously determined and their results confirmed by clinical studies which show that optimizing the dose to reach the PD targets leads to greater clinical efficacy [117].

Among lipid formulations, the clinical correlation of potential differences in PD has been difficult to establish because of limitations in determining MIC and differences in models of PK/PD indexes [116]. But, the study by Hong et al. [118], which included nine children diagnosed with fungal infection and treated with L-AMB, found that while C_{max}/MIC = 40 ± 13 produced a partial response, the complete response would need values of 67.9 ± 17 (p = 0.021). Considering the study by Andes et al. that reported D-AMB as five times more potent (C_{max}/MIC = 10), the results with L-AMB could be considered consistent [117].

Anyway, the pharmacokinetics of amphotericin B varies substantially between D-AMB, L-AMB, and ABLC, and its parameters should not be used to predict the behavior of any other AMB formulation [119]. The drug is poorly absorbed by the gastrointestinal tract and must be administered parenterally to treat systemic fungal infections.

As a fungicidal, amphotericin B relies on its concentration to display its antifungal effect. As mentioned before, the ability to reach those concentrations will determine the success of an intervention [120, 121].

According to the current manufacturer of D-AMB, an initial intravenous infusion of 1–5 mg/day gradually increased by 0.4–0.6 mg/kg/day produces C_{max} ranging from approximately 0.5 to 2 μg/mL, which stabilizes at about 0.5 μg/mL. D-AMB is highly bound to plasma proteins (> 90%) and has an initial half-life of 24 h and an elimination period of 15 days. About two-thirds of plasma concentrations are detected concomitantly in peritoneal, synovial, inflamed pleura, and aqueous fluids and rarely exceed 2.5% in cerebrospinal fluid. Highly resistant fungi may need higher interventions such as 1.5 mg/kg per day, with prolonged infusions over 6 h, compared with 4 h for susceptible species [122–126].

D-AMB concentrations in vitreous humor or normal amniotic fluid are negligible, whereas full details of its tissue distribution are not known. Excretion of the drug is slow though the kidneys, with less than 5% of the dose being eliminated in the active form. The accumulated urine output over a period of 7 days is equivalent to approximately 40% of the amount of drug infused [127].

Balancing the drug's kinetics along with its collateral effects, continuous infusion became one of the main strategies for the treatment of fungal infections with AMB, enhancing tolerability and lowering mortality, whilst reducing infusion-related toxicity [128–130].

LFABs, on the other hand, present a varied pattern in their pharmacokinetics, with primarily data obtained from animal studies. In 1989, Gondal et al. [131] reported peak concentrations five times higher compared to the same dosage of the conventional formulation, after administering 1 mg/kg of L-AMB to mice.

Subsequently, another study also indicated increased L-AMB concentrations in blood, liver, and spleen, while decreased levels were reported in kidneys and lungs [132]. In human beings, results described by Tollemar and Ringdén [133] showed that a dose of 3 mg/kg of the same compound obtained an average C_{max} of 24.3 μg/mL—in accordance with previous studies that reported even greater peaks, varying from 10 to 35 μg/mL [134, 135], but reaching lower concentrations than those produced by other LFABs in liver, spleen, lung, and kidneys—except for the central nervous system [50, 136]. After the administration of 5 mg/kg/day of liposomal amphotericin B, 90 μg/mL peak levels were measured, along with a half-life of 5–10 h [134].

It is presumed that the volume of distribution (V_d) of the liposome is limited by a decreased AMB interaction with membrane proteins and/or cholesterol, thus allowing significantly higher peak concentrations. However, the association of these higher concentrations to an increased antifungal action in vivo is still not determined [137]. Despite these data, the pharmacokinetics of L-AMB remains relatively unclear, but it is a fact

that a liposome composition has a significant impact on the properties of such formulations [138].

The first detailed profile of ABLC's disposition in human beings presented a broad interindividual variability, beyond large tissue distribution and a long-standing half-life time—similar to D-AMB. At standard doses, a C_{max} of 2 μg/mL was registered for the lipid complex [52, 136, 139].

The lipid complex of amphotericin B has a nonlinear dose-dependent kinetics, and, in contrast to the usual pattern, an increased clearance and V_d according to the dosage administered. In multiple schemes, with an interval smaller than $t_{1/2}$, there is little accumulation of the drug in the body [52]. As for tissue levels, different ratios are reported, according to the systems tracked: 0.2× (kidneys and brain), 2× (liver and lungs), and 5× (spleen), when compared to plasma concentrations [136].

Special populations such as pregnant women, elderly, and obese still lack pharmacokinetic studies on their activity [128]. As for neonates, preterm infants, and children, although there is extensive use on these age ranges, pharmacokinetic data and ideal dosage schemes are also scarce and limited, especially for infants under 10 kg [118, 140].

STRUCTURE–ACTIVITY RELATIONSHIP AND DRUG–TARGET INTERACTIONS

As a general rule, the polyenes exert their effect by associating with sterols of the fungal membrane and interrupting their integrity. This association occurs because of the high affinity between the drug and fungal ergosterol, which, after forming pores in its membrane, spills ions out of the cells, resulting in their death. Nevertheless, this affinity is less for human cholesterol, which explains the drug's greater effect on the pathogen than on host cells.

In 1988, Chéron et al. [141] were the pioneers in studying the correlation between AMB derivates and their biological activity. Such compounds represent a unique basis for the study of the antifungal structure–activity relationship and the understanding of its properties [142, 143]. Basically, the four axes that support its structure–activity relationship are (1) the derivation of a hydroxyl group at C-13; (2) the absence of a negative charge in the acid group; (3) the polyene itself; and (4) an ionizable nitrogen [144, 145].

The crucial role of mycosamine and the C-35-OH group in the antifungal activity of AMB has been demonstrated by Gray et al. [146]. They concluded that the antifungal mechanism of action of the drug is through a simple binding to the ergosterol of the fungi cells. However, a study by Tevyashova et al. [147] to evaluate several semi-synthetic derivates of AMB showed that those which contained the C-35-OH group and the mycosamine portion afforded low antifungal activity. This result was attributed to the decisive role of the hydroxyl group, especially its position in the region of C-7 to C-10, in the biological activity of AMB.

As for the hypothesis that the ergosterol binding is fundamental to the antifungal activity, a test performed with a derivate of AMB lacking the mycosamine portion suggested the capacity of the composition to bind to ergosterol, but not to form pores in the membrane. This research concluded that the direct interaction mediated by mycosamine between amphotericin B and ergosterol is necessary to form ion channels and cause the death of fungal cells [148]. Once again, Tevyashova et al. [147] obtained different results, suggesting that the mycosamine group does not play a critical role in the interaction with ergosterol. Therefore, the detailed mechanism of these interactions is not yet clear and needs to be investigated.

In its liposomal formulation, amphotericin B is integrated with the liposome membranes, forming a non-covalent complex between mycosamine (positively charge) and distearoylphosphatidylglycerol (DMPG) (negatively charged), as well as hydrophobic interactions. Liposomes accumulate at the site of infection, adhering to the surface of fungal cells, disintegrating and releasing AMB [149]. The amphotericin B lipid complex, on the other hand, depends on fungal lipases acting on the

formulation to then induce drug release in tissues [150].

MECHANISMS OF ACTION AND IMMUNE RESPONSE

After 60 years of investigation, the mechanisms of antifungal action of are not fully elucidated. However, there are ample consensus and evidence that AMB affects cells in two ways: via ergosterol binding and via oxidative damage.

Ergosterol Binding

Basically, the drug interacts with the lipid bilayer of the membrane through its hydrophobic domains resulting in multimeric pores that increase the permeability of ions (K^+, Ca^{2+}, and Mg^{2+}) and cause intracellular loss and consequent cell death.

The specific mechanisms of pore formation and the AMB membrane entrance remain very unclear. Baginski et al. [30] proposed two hypothetical pathways in which AMB–ergosterol binding can happen. The sequential mechanism assumes that the AMB monomers somehow enter the membrane and form binary complexes with the lipids found there, forming the channels. The one-step mechanism assumes that the AMB supramolecular complexes are first formed on the surface of the membrane and shortly after they enter the membrane, producing a reorganization towards the functional channels. Palacios et al. [151] also later described two different mechanisms for it: the sterol sequestration (membrane destabilization) and the membrane permeabilization (ion depletion).

It is clear that ergosterol is needed in a large number of cellular processes such as endocytosis, vacuole fusion, and stabilization of proteins, and that the formation of pores increases antifungal efficacy; however, it is not essential for the death of fungal cells, since the simple connection and sequestration of ergosterol to AMB is sufficient to damage cells because of the multiple cellular processes in which ergosterol is involved [152, 153]. Other studies corroborate this premise, demonstrating that not only is the formation of pores sufficient to produce cell death but that the chemical modifications in the AMB domains do not affect its antifungal activity [28, 154]. Finally, two studies argue that AMB is able to form channels even in the absence of sterols; however, both agree that the concentration required to form pores in these conditions is much higher than in the presence of sterols [155, 156].

Oxidative Damage

Early studies demonstrated that AMB induces oxidative stress in the cells [157, 158]. More recently, Liu et al. [159] confirmed this through genome-wide expression analysis showing that the drug induces the expression of stress genes. Many other independent studies have been performed but the precise role of AMB's oxidative damage in its antifungal activity remains undetermined [160–165].

Among the possibilities, AMB could act directly as a pro-oxidant and induce the accumulation of reactive oxygen species, which leads to influence of its mitochondrial activity, contributing to the oxidative burst. Consequently, the accumulation of free radicals induces multiple deleterious effects on the essential components of the cell, resulting in cell death [28].

In 1996, Brajtburg and Bolard [166] reported a compilation of revised information about the immunostimulatory properties of AMB. At first the drug induces an immune response predominantly in a proper dose range. The example used came from their study in which AMB increased the immune response in most inbred strains of mice. In addition, its prophylactic use against fungal infections would come from these assumptions, from stimulating the immune system under the appropriate conditions [167]. The article also highlights that although there are experimental studies agreeing with the stimulating effects of AMB on cells of the immune system, the suppression of humoral and cell-mediated immunity, as well as the suppression of macrophage activation, has also been reported.

Thus, the immunomodulatory effect also has been related to the AMB-associated toxicity. Suschek et al. [168] demonstrated that AMB increases the expression of the inducible nitric oxide synthase (iNOS) isoform, producing an increase in nitric oxide (implicated in the processes of vasodilation and protection against pathogens). However, AMB also increases the induction of pro-inflammatory cytokines and it would therefore be related to the drug's toxicity in the host [169].

What is known so far is that the drug interacts with Toll-like receptors (TLR2), inducing the release of pro-inflammatory cytokines including interleukin-6 (IL-6), IL-8, tumor necrosis factor (TNFα), and monocyte chemotactic protein 1 ((MCP-1). On the other hand, its interaction with TLR4 produces the release of IL-10, an anti-inflammatory cytokine [170]. In addition, the binding of AMB to sterols can activate membrane enzymes, such as NADPH oxidase, involved in the oxidative stress pathway, generating the accumulation of free radicals as previously described.

SPECTRUM OF ACTION

Literature about AMB's activity against different fungal specimens is conflicting. Despite being a well-known agent against a number of invasive infections, some clinical practice data support therapeutic failure in species like *Candida albicans* and *Candida parapsilosis* [171–174], previously considered to be fully susceptible [175, 176].

Susceptible

It is common sense that most yeasts and molds are susceptible to amphotericin B. Among the genus *Candida*, the species *Candida tropicalis*, *Candida krusei*, *Candida kefyr*, *Candida famata*, and *Candida guilliermondii* are all considered susceptible [171–174, 176]. In addition, *Cryptococcus neoformans*, *Malassezia* spp., *Saccharomyces cerevisiae, Aspergillus nidulans, Aspergillus niger*, and *Penicillium marneffei* are also designated as responsive [174, 176–179].

Intermediate

Aspergillus terreus, melanized fungi like *Bipolaris* spp., *Exophiala* spp., *Cladophialophora* spp., *Fonsecaea* spp. and *Phialophora* spp. among others, along with some *Paecilomyces* species are reported as intermediate in susceptibility [176–183].

Contradictory

Some inconsistent data is reported on *Scedosporium apiospermum, Aspergillus fumigatus, Aspergillus flavus*, *Trichosporon beigelii*, and *Fusarium* spp. regarding resistance in some isolates and treatment failures [176, 177, 180, 181, 184, 185]. On the other hand, *Candida lusitaniae* has been reported to be resistant; nevertheless, most strains were susceptible in the laboratory [171, 172, 174]. Additionally, difficult culture techniques or poor laboratory data also compromise the susceptibility appraisal, being reported for *Malassezia* spp. and Zygomycetes (*Absidia corymbifera*, *Apophysomyces elegans*, *Cunninghamella bertholletiae*, *Mucor* spp., *Rhizomucor pusillus*, *Rhizopus* spp., *Saksenaea vasiformis*) [180].

Resistant

Previously, *Scedosporium prolificans* and *Sporothrix schenckii* were reported as remarkable resistant species [181, 184, 185]. Nowadays, the most recent guidelines suggests caution with this therapeutic approach, because of other first-line options or limited data. The indication large remains for severe or disseminated disease or when the first-line treatment is unavailable [18, 19]. Among *Candida* species, *Candida auris*, *Candida haemulonii*, and *Candida lusitaniae* are considered resistant [186, 187].

OTHER THERAPEUTIC USES OF AMB

In addition to its antifungal action, evidence also supports the clinical use of amphotericin B in other contexts, as already well established in the treatment of visceral leishmaniasis (L-AMB

formulation), caused by the parasite *Leishmania* ssp. [188]. Its use on cutaneous and mucosal leishmaniasis, on the contrary, is still considered off-label by the US Food and Drug Administration (FDA) [188–191].

Evidence also points to antiprotozoal therapeutic applications with *Trypanosoma cruzi* epimastigotes and many reports with *Naegleria fowleri*, for example. Such reports also show that a mixed therapeutic approach could benefit the patient in both cases [157, 192, 193].

There are also studies that propose AMB as a promising new option as an antiviral agent, as it can affect the structure of cholesterol in viral envelopes and cell membranes, as well as in intracellular organelles. Data from experimental studies on the human immunodeficiency virus (HIV), Japanese encephalitis virus, as well as hepatitis B, herpes simplex, and rubella viruses have been reported [194–197].

MECHANISMS OF RESISTANCE

Fungal resistance mechanisms against AMB are rare, but have been reported, portraying a status where the patient does not respond to a standard therapeutic approach [198]. In 2014 Anderson et al. [199], in order to explain the paucity of clinically relevant microbial resistance against AMB, expanded the classic ion channel model and presented a sterol sponge model, in which AMB exists primarily in the form of an extra-membranous aggregates that physically extracts ergosterol from lipid bilayers. According to those authors, once the molecule may simultaneously perturb all of the cellular processes that depend on membrane ergosterol, a number of mutations would be necessary to provoke a relevant alteration, thus causing resistance [199].

Generally, there are host and microbial factors that interfere directly or indirectly with the immune response against a pathogen that predict the success of an intervention [200]. Important host factors are, for example, the immune status of the patient and presence of indwelling materials and surgical devices—possible vehicles for contaminations and biofilm development that could prevent sufficient concentrations of the drug reaching the infection site [201–203].

As for its mechanism of action, decreases in either the amount of ergosterol in the cell membrane or a change in the target lipid could compromise AMB's performance, as a result of decreasing binding sites [175, 198]. In the same way, any mutations in the ergosterol production pathway could affect the quality of this interaction, resulting in poor kinetics—such as *ERG* genes, required for ergosterol biosynthesis [200].

Candida albicans resistant to amphotericin B and fluconazole, for example, revealed upregulated *ERG5*, *ERG6*, and *ERG25* genes when compared with the wild-type strain. These mutations lead to an accumulation of sterol intermediates and a reduced affinity for AMB [204]. *ERG2* and *ERG3* mutations were also related, carrying a low ergosterol content [205–207]. Promastigotes of *Leishmania donovani* also highlight the importance of sterols, once their absence is related to resistance to amphotericin B [208]. Similar results were obtained from cultures of *C. tropicalis* and *Torulopsis glabrata* of a hematopoietic stem cell transplantation population [209]. *C. parapsilosis, C. lusitaniae, T. beigelii, Malassezia furfur, S. apiospermum, S. prolificans, Fusarium* spp., and some strains of *S. schenckii* also demonstrate primary resistance against amphotericin B as a result of those implications [175].

Oxidation resistance through increased catalase activity and incubation under hypoxia were credited for some *C. albicans, A. terreus*, and protoplasts cells [163, 210–212]. Additionally, biofilm formation was reported with *Candida* spp. [207]. Fatty acid composition was also proposed to explain polyene resistance, suggesting that an increased membrane fluidity could interfere with the interaction with amphotericin B. Nevertheless, no significant differences between mutants and wild types were tracked [213, 214]. Alterations of cell wall constituents such as chitin (*C. albicans, Kluyveromyces* spp., and *Schizosaccharomyces* spp.) and binding factors like glucans (*C. albicans, C. tropicalis, A. flavus*) could also determine resistance because of their preliminary role in polyene kinetics; notwithstanding, these

mechanisms are only partially understood [215–219].

Finally, as ergosterol plays an essential role in the yeast cell cycle, stationary-phase cells were related to increased resistance in the exponential phase, a fact that could be associated with reduced chitin synthase activity in the stationary growth phase [216, 220, 221].

Resistance against amphotericin B during therapy is not common and is attributed to an acquired resistance of the pathogen or co-infection with different species [175]. In particular, patients with severe neutropenia or compromised hematopoietic health are likely to face this impasse [222, 223]. Cases of *C. albicans, Candida rugosa, C. lusitaniae*, and *C. guilliermondii* were reported [224–226].

STABILITY

According to the literature, reports of amphotericin B's instability when submitted to unfavorable conditions such as exposure to heat, light, and low pH are commonly found [227]; it is even among the 110 substances liable to degradation in tropical conditions (50 °C and 100% humidity) listed by the World Health Organization (WHO) [228]. Aqueous solutions of AMB, on the contrary, could be more stable for prolonged periods of air and light exposure, if maintained between pH 4 and 10 [23, 229].

A recent study showed insignificant degradation of AMB in the presence of water [230]; this fact could be related to AMB's low solubility in aqueous and neutral pH vehicles. Exposure of AMB to ± 70 °C for up to 7 days did not provoke thermal degradation. In a photolysis experiment, degradation occurred within 7 min after exposition to light, in agreement with previous studies that assessed AMB's stability in dark environments [231].

Wiest et al. [232] documented the stability of amphotericin B (100 μg/mL) in four different concentrations of dextrose injection (5%, 10%, 15%, and 20%), when stored for up to 24 h at 15–25 °C and protected from light. This study raised an important question regarding the administration of the drug in dextrose solutions, with concentrations greater than 5%, which would minimize nutritional deficits and glucose instability in neonates.

Regarding the LFABs, the liposome stability is guaranteed by their small size and the fact that cholesterol and DMPG exhibit a high transition temperature (55 °C), when the preparation naturally tends to collapse, releasing its content [128, 233]. The lipid complex, with its two phospholipids, distestylylphosphatidylcholine (DMPC) and DMPG, has a transition temperature of 23 °C (below body temperature), which suggests that the preparation may disintegrate before reaching the site of action [233].

BIOEQUIVALANCE OR THERAPEUTIC EQUIVALANCE

Pharmacologically, two preparations are considered equivalent if they present the same qualitative and quantitative composition of active ingredients and the same pharmaceutical form. Two pharmaceutical equivalents are defined as bioequivalent when, after administration of the same dosage, their bioavailability does not differ statistically. Once two equivalent pharmaceutical forms are also bioequivalent, theoretically, they can be considered as therapeutically equivalent [233].

With the advent of lipid formulations and the fact that they are related to reduction of toxicity, it became necessary to control these drugs to guarantee the level of tolerance and effectiveness, since any change in manufacturing may affect drug performance [24]. It is known that the lipid composition, charge, and size of these preparations can vary considerably depending on the manufacturer [137]. For instance, the manufacturer of ABLC informs in the package insert that liposomal encapsulation or incorporation in a lipid complex can substantially affect the functional properties of the drug by differing in the chemical composition and physical form of the lipid component [234], which, therefore, already attests to its non-bioequivalence.

In vitro [235] and in vivo animal studies [236] sought to establish a therapeutic

equivalence of the conventional formulation compared to that associated with liposomes, claiming that both had the same antifungal potency. However, it is still questioned whether such preclinical bioequivalence data can be extrapolated in humans. Heinemann et al. [137] discussed the need to demonstrate that a dosage of D-AMB of 1 mg/kg would in fact equate to the same antifungal activity as a dose of L-AMB of 1 mg/kg.

Recently, a study gathered evidence and confirmed that LFABs are not therapeutically equivalent [233]. L-AMB and ABLC data are exposed in relation to C_{max} and area under the curve (AUC), showing evident differences between them (non-standard confidence interval of 90%), once again opposing the definition of bioequivalence.

Yet, recommendations of scientific associations and guidelines clearly state the differences between LFABs when presenting their evidence grid in the treatment of different fungal infections. The guidelines of the Infectious Diseases Society of America (IDSA) declare that L-AMB and ABLC have the same spectrum of activity as D-AMB; however, they have distinct pharmacological properties and frequencies of adverse events [237].

Finally, Cifani et al. [233] summarized why lipid formulations cannot be considered therapeutically equivalent. First, because the preparations are not bioequivalent. Second, because there are not enough controlled clinical trials that compare the effectiveness of the formulations in question. Last of all, because therapeutic equivalence is not supported by worldwide guidelines and consensus as different recommendations are attributed to lipid formulations of amphotericin B in their recommendations.

ASPECTS RELEVANT TO CLINICAL PRACTICE

In the daily routine, AMB is an important resource in severe fungal infections, available as a useful agent against virulent infections such as *A. flavus* and *Scedosporium* spp., often related to refractoriness [238].

Data suggests different applications for the different formulations of AMB, including primary and secondary prophylaxis and in refractory disease, when aspergillosis is suspected or confirmed. As a primary prophylaxis, data supports the use of AMB in hematological malignancies (acute myeloid leukemia with prolonged neutropenia [239–244], acute lymphoblastic leukemia [245], allogeneic hematopoietic stem cell transplantation, HSCT [240]), as a result of a high-risk neutropenic status; invasive infections of the central nervous system [63, 64, 76, 243], pulmonary and extrapulmonary disease [63].

As a secondary prophylaxis, patients with previous invasive infections and undergoing allogeneic HSCT or entering a risk period with non-resectable foci of *Aspergillus* disease benefit from L-AMB [246, 247]. Whereas patients with refractory hematological disease had an improved survival rate with L-AMB 3–5 mg/kg [58, 248, 249] and ABLC 5 mg/kg [238, 249–251].

Amphotericin B toxicity is the barrier that prevents its proper prescription, which can result in the spread of infections and therapy failure [136]. In addition, acute infusion-related reactions often imply the interruption of a complete course of the medication. In this sense, LFABs have brought a significant advance in the treatment of invasive fungal infections, allowing prolonged and higher dosage use when compared to D-AMB. Such formulations have often been used interchangeably, although constant vigilance is necessary given the possibility of significant differences in their effectiveness. One question that remains concerns access to such formulations, since the high cost significantly limits their use in developing countries.

COMBINATION ANTIFUNGAL THERAPY

The application of combined antifungal therapy (CAF) is widely accepted to maximize the antifungal effect through the synergistic effect by attacking the same or different targets in fungal cells [252]. As advantages, in addition to the

Table 2 Evidence-based use of combined antifungal therapy for some fungal diseases

Fungal disease	CAF	Recommendation	References
Invasive aspergillosis	AMB + echinocandin	Patients with hematological malignancies and an elevated galactomannan level Salvage therapy in high-risk patients	[237, 255, 256]
Candidiasis	AMB + flucytosine AMB + fluconazole	Native valve endocarditis; candida CNS infection; azole-resistant *Candida glabrata*, ascending pyelonephritis and fluconazole-resistant candida endophthalmitis	[51, 257]
Cryptococcosis	AMB + flucytosine AMB + fluconazole	CNS cryptococcal infections, especially in HIV-infected patients; transplantation	[258–260]
Mucormycosis	AMB + echinocandin AMB + azoles	Refractory disease	[16]

AMB amphotericin B, *CNS* central nervous system

synergistic effect, the amplitude in the spectrum of action, less risk of toxicity owing to the reduction of the combined doses, and less probability of resistance or tolerance (even without evidence to support this statement) can be mentioned. As disadvantages, antagonistic adverse reactions should be considered, in addition to the higher costs and the possibility of systemic toxicity due to the accumulation of more than one antifungal in the body [253, 254].

Drug interactions (whether synergistic or antagonistic) depend on the type of preparations used in a CAF, on the genus and species of fungi, and, of course, on the timing of drug administration and their doses [252]. Table 2 summarizes the available data on the use of amphotericin B in combination therapy, currently recommended in clinical practice.

FUTURE PERSPECTIVES

Despite the broad spectrum of fungicidal activity, limitations such as parenteral administration, reactions related to infusion, acute and chronic toxicity, and also the dosage limits end up harming the potential clinical use of AMB. Although LFABs exhibit a more favorable tolerability and toxicity profile, they are not free of side effects.

The development of non-invasive formulations of AMB is very challenging because of its low aqueous solubility in physiological pH, permeability through membranes, and tendency to self-aggregate, in addition to its low stability at high temperatures and acid pH [261].

Progress in the development of a new formulation of AMB has been described in the literature, with emphasis on encochleated amphotericin B (Coch-AmB). It is a new formulation composed of phospholipid bilayers precipitated with bivalent cations in a multilayer structure, wrapped in a spiral without internal watery space. Such a structure protects the molecule inside, which makes it more stable and allows its oral administration. The drug is released after the interaction of this new system with the target cells, which open in the presence of low concentrations of intracellular calcium [262].

This new possibility would bring numerous advantages to clinical practice including the avoidance of unnecessary patient hospitalization, expansion of antifungal therapy to developing countries where access to hospitals is

Table 3 Current clinical trials with new approaches to amphotericin B

CTID	Title	Phase	Situation	Last update	Outcome measures	Source
jRCTs041200022	Preoperative eradication of *Candida* colonization using amphotericin B for surgical site infections after high-level HBP surgeries: a phase III randomized parallel-group trial	–	Recruiting	Jun/2020	1. Comparisons of surgical site infections incidence between *Candida* eradication group and non-eradication group - None was reported	http://www.rctportal.niph.go.jp
NCT02273661	Evaluation of a therapeutic strategy including nebulized liposomal amphotericin B (Ambisome®) in maintenance treatment of allergic bronchopulmonary aspergillosis (cystic fibrosis excluded)	II	Completed	Jun/2020	1. Occurrence of first severe clinical exacerbation within 24 months following the attack treatment defined by the onset or worsening of dyspnea aggravating the baseline condition that justified (1) increased inhalation treatments, (2) and/or initiation of systemic corticosteroid treatment (3) and/or hospitalization (4) persisting for more than 7 days – None was reported	http://www.clinicaltrials.gov
NCT03399955	Short course regimens for treatment of PKDL (Sudan)	II	Recruiting	Jan/2020	1. Definitive cure and incidence of treatment-emergent adverse events – None was reported	http://www.clinicaltrials.gov
NCT04031833	Encochleated oral amphotericin for cryptococcal meningitis trial (EnACT)	I/II	Recruiting	Nov/2019	1. Highest dose tolerated without inducing vomiting and evidence of fungicidal activity – None was reported	http://www.clinicaltrials.gov

Table 3 continued

CTID	Title	Phase	Situation	Last update	Outcome measures	Source
NCT04140461	AMB dose for cryptococcal meningitis	III	Not yet recruiting	Oct/2019	1. Number of subjects died at week 48 2. 2-week negative culture and disability – None was reported	http://www.clinicaltrials.gov
NCT02629419	CAMB/MAT2203 in patients with mucocutaneous candidiasis	II	Active, not recruiting	Oct/2019	1. Symptoms of mucocutaneous candidiasis 2. Area under the plasma concentration versus time curve (AUC) 3. Drug concentrations in plasma, urine, and saliva 4. Adverse events, changes in laboratory parameters 5. Other outcomes: long-term adverse events, changes in laboratory parameters 6. Long-term symptoms of mucocutaneous candidiasis – None was reported	http://www.clinicaltrials.gov

Table 3 continued

CTID	Title	Phase	Situation	Last update	Outcome measures	Source
NCT02283905	Amphotericin B and voriconazole for pulmonary blastomycosis	IV	Recruiting	Sep/2019	1. The concentration–time profile of antifungals during treatment relative to the level of susceptibility of the infecting organism 2. Clinical recovery—as assessed by time to defervescence; and white blood cell (WBC) count resolution 3. Clinical recovery—time to discontinuation of mechanical ventilation 4. Clinical recovery—time to respiratory dysfunction resolution – None was reported	http://www.clinicaltrials.gov
NCT04018417	Evaluation of amphotericin B in Optisol-GS for prevention of post-keratoplasty fungal infections	II/III	Withdrawn	Jul/2019	1. Endothelial cell density 2. Incidence of post-keratoplasty fungal keratitis – None was reported	http://www.clinicaltrials.gov

AMB amphotericin Bl, *CTID* clinical trial identification, *HBP* hepato-biliary-pancreatic, *PKDL* post-kala-azar dermal leishmaniasis, *CAMB/MAT2203* encochleated amphotericin B, *HIV* human immunodeficiency virus

difficult, prophylactic use of AMB, lack of side effects related to the infusion, and accessibility to treatment. Finally, with the slower release of the active ingredient, higher concentrations could be achieved in several organs. Table 3 displays the list of the clinical trials from the last 2 years that seek to improve the use of amphotericin B in different situations.

CONCLUSIONS

In the 60 years since it was first marketed, amphotericin B remains the gold standard for the treatment of invasive fungal infections while its lipid formulations have been developed to improve tolerability with a similar spectrum of activity and a more favorable safety profile. However, they have considerably different pharmacological characteristics. Both

ABLC and L-AMB have a distinguished pharmacokinetic profile that determines their efficacy and toxicity. On the other hand, the amphotericin B lipid complex, with a larger particle size, is characterized by a rapid decline in the concentration of AMB after intravenous administration, followed by an extended elimination half-life which contrasts with the higher C_{max} values and AUC, lower volume of distribution, and shorter elimination half-life of the liposomal version.

Even though some experimental tests have been published, guidelines for better bioequivalence studies are lacking since it is essential to characterize both the stability and the pharmacokinetic profile of LFABs and thus ensure that not only patients benefit from these formulations but that professionals are safe to use them.

The development and registration of new formulations that bring improvements in pharmacological and biopharmaceutical characteristics represent expensive and time-consuming tasks but are essential to reduce toxicity and improve drug tolerability. Promising clinical trials stimulate new possibilities for amphotericin B. The goal will be achieved when AMB can be widely distribute at a lower cost and in a non-parenteral version, resulting in numerous benefits for end users.

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