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REVIEW ARTICLE

Amphotericin B Formulations: A Comparative Review of Efficacy and Toxicity

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Abstract Because of the increasing prevalence and changing microbiological spectrum of invasive fungal infections, some form of amphotericin B still provides the most reliable and broad spectrum therapeutic alternative. However, the use of amphotericin B deoxycholate is accompanied by dose-limited toxicities, most importantly, infusion-related reactions and nephrotoxicity. In an attempt to improve the therapeutic index of amphotericin B, three lipid-associated formulations were developed, including amphotericin B lipid complex (ABLC), liposomal amphotericin B (L-AmB), and amphotericin B colloidal dispersion (ABCD). The lipid composition of all three of these preparations differs considerably and contributes to substantially different pharmacokinetic parameters. ABLC is the largest of the lipid preparations. Because of its size, it is taken up rapidly by macrophages and becomes sequestered in tissues of the mononuclear phagocyte system such as the liver and spleen. Consequently, compared with the conventional formulation, it has lower circulating amphotericin B serum concentrations, reflected in a marked increase in volume of distribution and clearance. Lung levels are considerably higher than those achieved with other lipid-associated preparations. The recommended therapeutic dose of ABLC is 5 mg/kg/day. Because of its small size and negative charge, L-AmB avoids substantial recognition and uptake by the mononuclear phagocyte system. Therefore, a single dose of L-AmB results in a much higher peak plasma level (C_{max}) than conventional amphotericin B deoxycholate and a much larger area under the concentration–time curve. Tissue concentrations in patients receiving L-AmB tend to be highest in the liver and spleen and much lower in kidneys and lung. Recommended therapeutic dosages are 3–6 mg/kg/day. After intravenous infusion, ABCD complexes remain largely intact and are rapidly removed from the circulation by cells of the macrophage phagocyte system. On a milligram-to-milligram basis, the C_{max} achieved is lower than that attained by conventional amphotericin B, although the larger doses of ABCD that are administered produce an absolute level that is similar to amphotericin B. ABCD exhibits dose-limiting, infusion-related toxicities; consequently, the administered dosages should not exceed 3–4 mg/kg/day. The few comparative clinical trials that have been completed with the lipid-associated formulations have not demonstrated important clinical differences among these agents and amphotericin B for efficacy, although there are significant safety benefits of the lipid products. Furthermore, only one published trial has ever compared one lipid product against another for any indication. The results of these trials are particularly difficult to interpret because of major heterogeneities in study design, disease definitions, drug dosages, differences in clinical and microbiological endpoints as well as specific outcomes examined. Nevertheless, it is possible to derive some general conclusions given the available data. The most commonly studied syndrome has been empiric therapy for febrile neutropenic patients, where the lipid-associated preparations did not appear to provide a survival benefit over conventional amphotericin B deoxycholate, but did offer a significant advantage for the prevention of various breakthrough invasive fungal infections. For treatment of documented invasive fungal infections that usually involved hematological malignancy patients, no individual

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randomized trial has demonstrated a mortality benefit due to therapy with one of the lipid formulations. Results from meta-analyses have been contradictory, with one demonstrating a mortality benefit from all-cause mortality and one that did not demonstrate a mortality benefit. In the only published study to examine HIV-infected patients with disseminated histoplasmosis, clinical success and mortality were significantly better with L-AmB compared with amphotericin B deoxycholate; there were no differences in microbiological outcomes between treatment groups. The lipid-associated preparations were not significantly better than amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis for either clinical or microbiological outcomes that were studied. In all of the trials that specifically examined renal toxicity, the lipid-associated formulations were significantly less nephrotoxic than amphotericin B deoxycholate. Infusion-related reactions occurred less frequently with L-AmB when compared with amphotericin B deoxycholate; however, ABCD had equivalent or more frequent infusion-related reactions than conventional amphotericin B, and this resulted in the cessation of at least one clinical trial. At the present time, this particular lipid formulation is no longer commercially available. For the treatment of most invasive fungal infections, an amphotericin B lipid formulation provides a safer alternative than conventional amphotericin B, with at least equivalent efficacy. As the cost of therapy with these agents continues to decline, these drugs will likely maintain their important role in the antifungal drug armamentarium because of their efficacy and improved safety profile.

1 Introduction

Invasive fungal infections are becoming increasingly recognized as major causes of morbidity and mortality in immunocompromised hosts. The mortality rate of some of these invasive fungal diseases exceeds 60 % in certain situations, and is one of the greatest challenges facing clinicians who care for immunosuppressed patients. Moreover, an increasing diversity of fungal species has been described in this population [1–3]. The early diagnosis of systemic fungal infections in these immunologically impaired individuals remains problematic because of the lack of sensitivity of available diagnostic tests. Consequently, antifungal therapy is frequently administered empirically for presumptive invasive fungal infections in these patients until definitive identification of the causative species and antifungal susceptibility profiles are available. Unfortunately, no ideal antifungal agent exists. Recently, newer agents to treat invasive fungal infections have become available, including the azoles and echinocandins. These drugs lack the toxicity of previously available agents, but issues related to pharmacokinetics, drug interactions, spectrum of activity, and limited routes of administration restrict their usefulness. Historically, amphotericin B has been considered the 'gold standard' among antifungal drugs, and it remains the agent with the broadest antifungal spectrum; however, its use is hampered by a high incidence of infusion-related adverse events and a substantial incidence of renal toxicity; these toxicities frequently render the conventional formulation of amphotericin B deoxycholate unsuitable for treatment. Lipid formulations of amphotericin B have been developed to address the toxicity issues associated with conventional amphotericin B deoxycholate; however, the relative efficacy and safety of these agents has not been adequately studied. The purpose of this review is to examine the available published human pharmacokinetic and comparative clinical data to derive some conclusions regarding these questions.

1.1 Literature Search Strategy

Articles were identified in PubMed that were published from 1977 until 1 September 2012. All identified articles and the cited references were examined to detect additional relevant references. Search terms that were used, singly and in combination, included 'amphotericin', 'amphotericin B', 'amphotericin B deoxycholate', 'amphotericin B formulations', 'lipid-associated amphotericin B', lipid-complexed amphotericin B', 'amphotericin B lipid', 'amphotericin B liposomal', 'liposomal amphotericin B', 'amphotericin B lipid complex', 'ABLC', 'Abelcet', 'amphotericin B colloidal dispersion', 'ABCD', 'Amphotec', 'Amphocil', 'amphotericin B nephrotoxicity', 'infusion-related reactions', 'amphotericin B pharmacokinetics', 'cryptococcal meningitis', 'invasive aspergillosis', 'neutropenic fever', 'febrile neutropenia', empiric therapy of febrile neutropenia', 'histoplasmosis', and 'leishmaniasis'. Emphasis was placed on review of published clinical trials that compared amphotericin B deoxycholate and the various commercially available lipid preparations of amphotericin B, which included liposomal amphotericin B (L-AmB), amphotericin B lipid complex (ABLC) and amphotericin B colloidal dispersion (ABCD).

2 Amphotericin B Chemistry and Pharmacokinetics

Amphotericin B is a macrolide polyene antifungal agent that is produced through a fermentative process by the soil actinomycete, *Streptomyces nodosus*. It has been available for clinical use since its initial FDA approval in 1959. Amphotericin B itself is insoluble in saline at a normal pH; consequently, it is formulated as a mixture of 50 mg

Table 1 Physical characteristics and pharmacokinetic properties of amphotericin B preparations

Property	Amphotericin B formulation			
	Amphotericin B deoxycholate	L-AmB	ABLC	ABCD
Composition	–	HSPC:cholesterol:DSPG 10:5:4	DMPC:DMPG 7:3	Cholesteryl sulfate
Structure	Micelles	Unilamellar spherical liposomes	Ribbons	Discs
Amphotericin B:lipid ratio	NA	1:9	1:3	1:1
Size (nm)	0.035	80	1,600–11,000	122 × 4
Dose (mg/kg)	1.0	5.0	5.0	4.0
C_{max} (μg/mL)	1.5–2.9	83 ± 35.2	1.7	2.9
AUC (μg · h/mL)	17.1–36	555 ± 311	14.0 ± 7.0	36
Half-life (h)	24	8.6 ± 3.1	173.4	28.2
V_d (L/kg)	5.0 ± 2.8	0.16	131 ± 57.7	4.1
Cl (mL/h/kg)	38.0 ± 15.0	11.0 ± 6.0	436 ± 188	112

Data derived predominately from package inserts

± indicates range of values

ABCD amphotericin B colloidal dispersion, *ABLC* amphotericin B lipid complex, *AUC* area under the concentration–time curve, *Cl* clearance, C_{max} peak plasma concentration, *DMPC* dimyristoyl phosphatidylcholine, *DMPG* dimyristoyl phosphatidylglycerol, *DSPG* distearoyl phosphatidylglycerol, *HSPC* hydrogenated soy phosphatidylcholine, *L-AmB* liposomal amphotericin B, *NA* not applicable, V_d volume of distribution

amphotericin B along with 41 mg of the detergent, sodium deoxycholate, which results in ribbon-like aggregates that form a mixed colloidal dispersion [4].

Upon intravenous infusion, amphotericin B immediately dissociates from the deoxycholate and rapidly becomes 95–99 % bound to plasma lipoproteins, initially divided between the high-density lipoprotein (HDL) and low-density lipoprotein (LDL) fractions. A much greater proportion binds to HDLs with a subsequent equilibrium shift to the LDL fraction through the action of the cholesterol ester transfer protein or lipid transfer protein (LTP) [5]. It appears that the distribution of unbound amphotericin B into the serum lipoproteins may be related to LTP-facilitated distribution of esterified cholesterol from HDL to LDL.

After initial infusion of 1 mg/kg, a peak serum concentration (C_{max}) of approximately 1.5–2.0 mg/L is achieved, with a corresponding volume of distribution (V_d) of about 2.4–4.0 L/kg (Table 1). Amphotericin B demonstrates a triphasic plasma profile [6]. The initial plasma half-life varies between 24–48 h, with about 2–5 % of the unchanged drug being excreted in the urine within 24 h, along with a small amount in feces. It has a very long elimination half-life of at least 15 days, with substantial levels accumulating in the liver and spleen and to a lesser extent the lungs and kidneys (Table 2) [7, 8]. The terminal elimination phase contains about 80 % of the total area under the concentration–time curve (AUC) of amphotericin B, with one-third of the total clearance being renal and 42.5 % in feces as unchanged drug; humans do not metabolize amphotericin B to any extent. Total recovery of drug is about 93.4 % [6].

Table 2 Tissue levels (μg/g) of amphotericin B with different formulations

Organ	Amphotericin B deoxycholate	L-AmB	ABLC	ABCD
Liver	93.2	175.7	196.0	94.4
Spleen	59.3	201.5	290.0	81.3
Lung	12.9	16.8	222.0	32.6
Kidney	18.9	22.8	6.9	36.7
Brain	–	0.56	1.6	1.39

Data from references [7] and [8]

ABCD amphotericin B colloidal dispersion, *ABLC* amphotericin B lipid complex, *L-AmB* liposomal amphotericin B

2.1 Antifungal Mechanism of Activity

The antifungal mechanism of action of amphotericin B involves preferential binding to ergosterol, the principal component of the fungal cell membrane. The amphotericin B molecule is composed of two domains, a hydrophobic (polyene hydrocarbon chain) and a hydrophilic (polyhydroxyl chain) region, which are important for its antifungal effect. Approximately eight amphotericin B molecules hydrophobically interact via the polyene chain with eight ergosterol molecules, which results in the formation of pores that consist of two 'barrels' of hydrogen bonded end-to-end, with each of the barrels consisting of eight polyene monomers arranged circumferentially like staves in a barrel [9]. The hydrophilic polyhydroxyl chains face the interior of the pore. This pore formation results in the rapid efflux of K^+, inhibition of fungal glycolysis and subsequent Mg^{2+} efflux. These losses, along with a

subsequent influx of protons into the fungal cell, cause acidification of the fungal interior with precipitation of the cytoplasm and ultimate cell death.

Despite having been in clinical use for over 50 years, amphotericin B continues to exhibit very good in vitro activity against a broad spectrum of clinically relevant fungal isolates, including most strains of *Candida* spp., *Aspergillus* spp., and most other filamentous fungi, such as the *Mucorales.* Although antifungal resistance has been demonstrated very infrequently, some well recognized species do demonstrate intrinsic resistance to amphotericin B, including *Aspergillus terreus* [10], *Fusarium* spp. [11], *Scedosporium* spp. [12], and *Trichosporon asahii* [13–15], or exhibit phenotypic switching to amphotericin-resistant isolates when exposed to drug pressure, as seen with *Candida lusitaniae* [16].

In vitro, amphotericin B demonstrates concentration-dependent killing against a wide range of fungi [17]. Consequently, fungicidal activity could potentially be maximized by administering large doses of the drug in an effort to optimize the C_{max}/minimum inhibitory concentration (MIC) ratio; unfortunately, dose-related toxicities of amphotericin B make this strategy impractical.

3 Amphotericin B-Associated Toxicity

The major factor limiting the use of amphotericin B deoxycholate is toxicity, which is manifested as acute infusion-related reactions and dose-related nephrotoxicity. In fact, the dose-related toxicity of amphotericin B usually limits the maximal tolerated dose to 0.7–1.0 mg/kg/day, a dosage that may be suboptimal for clinical success against invasive fungi in compromised hosts.

Infusion-related toxicities associated with amphotericin B include fever and chills, rigors, arthralgias, nausea, vomiting and headaches. Because amphotericin B is a microbial product, it is recognized by Toll-like receptor (TLR) 2 and the transmembrane signaling protein CD14 on the surface of mononuclear cells [18, 19]. Through intracellular signaling pathways that include the adapter protein MyD88 and nuclear factor κB, amphotericin B induces the expression of pro-inflammatory cytokine genes, including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-6, IL-1ra and the chemokines IL-8, monocyte chemotactic protein (MCP)-1, and macrophage inflammatory protein (MIP)-1β, which are thought to be the principal causes of the acute infusion-related toxicities associated with amphotericin B [18, 20–22]. Amphotericin B deoxycholate-induced synthesis of IL-1β occurs between 2 and 6 h, similar to the clinically observed time interval noted in actual patients who are receiving the drug and experiencing infusion-related events [19]. A number of pre-treatment regimens, including non-steroidal anti-inflammatory agents, antihistamines, meperidine, and corticosteroids, have been administered in an attempt to ameliorate these reactions; however, the actual benefits of most of these maneuvers are uncertain [23].

Following infusion of amphotericin B, there is a rapid vasoconstrictive effect on the afferent renal arterioles, causing a decrease in renal blood flow and a decrease in the glomerular filtration rate [24]. Furthermore, although amphotericin B has a tenfold greater affinity for binding to the fungal ergosterol ($K_d = 6.9 \times 10^5$) than to the cholesterol of the mammalian cell membranes ($K_d = 5.2 \times 10^4$), non-selective disruption of mammalian cells does occur [25]. It is likely that the basis for most of the renal toxicity regularly associated with amphotericin B results from a higher relative exposure of the drug to renal cells [25, 26]. Renal tubular cell uptake of amphotericin B is thought to result from LDL receptor-mediated endocytosis of the serum LDL-amphotericin B complexes, due to a relative abundance of LDL receptors on renal tubular cells and paucity of HDL receptors [27, 28].

3.1 Clinical Significance of Amphotericin-Induced Nephrotoxicity

The burden of amphotericin B-induced nephrotoxicity can be substantial in certain patient populations. In a study by Wingard et al. [29] of patients treated with amphotericin B for invasive aspergillosis, 53 % developed nephrotoxicity, defined as a doubling of the serum creatinine. Of those who had amphotericin B-induced renal dysfunction, 15 % ultimately required dialysis, particularly if they were receiving other nephrotoxic agents, such as cyclosporine. In those whose creatinine value was elevated above 2.5 mg/dL, 38 % ultimately required dialysis. Moreover, receipt of dialysis was associated with a threefold risk of death [29].

In another study, which examined 707 patients who received parenteral amphotericin B deoxycholate therapy, 30 % developed acute renal failure [30]. When renal dysfunction occurred, the mortality rate was much higher, 54 versus 16 % in those who did not develop renal failure (odds of death = 6.6). The mean adjusted increase in length of stay was 8.2 days, and the adjusted total cost was $29,823 (in 2001 US$) in patients who developed nephrotoxicity [30].

A third study evaluated the economic effects of amphotericin B-induced nephrotoxicity in a 9-year study that involved 494 patients treated with conventional amphotericin B [31]. During this study period, the rate of nephrotoxicity was 12 %. The development of nephrotoxicity was associated with a 2.7-fold higher risk of death ($p < 0.001$). However, the authors of this study could not detect an impact on calculated hospitalization costs or

length of stay in the hospital if nephrotoxicity developed, which contrasts with the results of the previously described study [30]. Therefore, nephrotoxicity occurs regularly in patients treated with conventional amphotericin B deoxycholate. It is associated with substantial morbidity, most importantly, the need for dialysis, which results in an approximately threefold increase in mortality and likely increased medical care costs. Consequently, there is an important need for alternative means to decrease amphotericin B-associated nephrotoxicity.

4 Lipid-Associated Formulations of Amphotericin B

In order to attenuate its toxicity and increase the therapeutic potential, alternative formulations of amphotericin B have been developed and incorporated into regular clinical use [7, 32–40]. The molecular structure of amphotericin B deoxycholate, which results in poor water solubility and excellent lipid solubility, makes the drug an ideal candidate for incorporation into lipid-based preparations. Lipoprotein association of drug compounds can significantly influence not only their pharmacological and pharmacokinetic properties, but also their relative toxicity [35, 41]. Lipid-formulated preparations provide several potential advantages when compared with native amphotericin B: [36] (1) a poorly soluble drug, like conventional amphotericin B deoxycholate, can be prepared more easily for parenteral infusion if associated with lipids; (2) lipid bilayer encapsulation likely protects the drug from destruction by enzymatic degradation and/or host immune factor inactivation; (3) liposomes alter the pharmacokinetic profile of the agent by slowly releasing amphotericin B, resulting in diversion from potentially vulnerable tissues, most importantly, the kidney; (4) the composition of the lipid-carrier ensures that amphotericin B remains associated with the carrier, preventing uncontrolled drug leakage, and is thus unavailable to interact with mammalian cells to exert its toxic effects; and (5) association with the lipid-carrier facilitates uptake of the complex by the circulating monocytes as well as other cells of the mononuclear phagocyte system, so drug delivery can be targeted to desired sites of infection, improving the efficiency of delivery. Selective transfer of the antifungal agent from the donor lipid to the fungal cell membrane may then occur [5, 27]. Multiple laboratory animal studies and human data indicate that lipid amphotericin B preparations achieve quantifiable concentrations in the liver, spleen, and lung tissue, sites frequently involved by opportunistic fungal infections [8, 33, 40, 42].

When lipid vesicles are infused, the kinetics and distribution of the drug are mainly dictated by the behavior of the vesicles. These vesicles are largely constrained to remain within the vasculature, and are able to exit in only a few specialized sites, such as the liver or spleen, where there is fenestrated capillary endothelium or, alternatively, where the endothelium is disrupted by necrosis or inflammation due to infection. Consequently, it is predictable that incorporation of a drug like amphotericin B into the vesicle will augment drug uptake by the liver and spleen and cause accumulation of the drug in elements of the mononuclear phagocyte system and at sites of capillary damage and inflammation [43]. The pharmacokinetics and dispersion of lipid-based amphotericin are strongly determined by its physicochemical characteristics such as particle size, the surface electrostatic charge of the lipid material, the rigidity of the lipid bilayer, and the amount of incorporated lipid material [32]. Smaller liposomes (e.g., L-AmB) tend to have longer circulating half-lives because they are not readily recognized and taken up by the mononuclear phagocyte system. In the liver, for instance, they can extravasate through fenestrations of the hepatic sinusoids and interact with hepatocytes, thus avoiding phagocytic ingestion by Kupfer cells [32]. A similar process probably occurs in the lungs. On the other hand, larger lipid compounds (e.g., ABLC), because of their size, are readily recognized by the mononuclear phagocytic system and rapidly ingested.

Increasing the phospholipid bilayer rigidity can decrease the permeability of the liposome's membrane and avoid the early release of free drug. Cholesterol has been added to the bilayer in some of the preparations, making them less sensitive to degradation through exchange of liposome constituents with plasma lipoproteins [32].

Phospholipids used in lipid preparations can have positive (stearylamine), negative (dimyristoyl phosphatidylglycerol) or neutral charges (dimyristoyl phosphatidylcholine). The presence of charged liposomes causes the reduction of LTP-mediated transfer of lipids from HDL and LDL and is likely responsible for the predominant distribution of amphotericin B into the HDL fraction [27]. As a result, lipid-amphotericin B complexes are diverted from renal tubular cells because of their relative lack of HDL receptors [26]. This concept, that the lipid preparations prevent amphotericin B binding to the kidneys and selective distribution to other tissues, appears to explain the diminution of toxicity of the lipid-based formulations [36].

The availability of amphotericin B at sites of infection may be accounted for by (1) capillary leakage at the site; (2) phagocytic uptake of drug at site; or (3) transport by mononuclear phagocytes to infected locations. Once delivered to the site of infection, lipid-associated amphotericin B appears to be equally toxic to fungal cells as is conventional HDL- or LDL-associated drug [27]; consequently, even though the lipid-formulated drugs are less toxic to mammalian cells, the associated amphotericin B

still retains its fungicidal activity. Table 2 provides levels of amphotericin B achieved in various tissues after administration of the different preparations. Because the types of patients from which these data were derived were so heterogeneous with regard to underlying diseases and duration of antifungal therapy, it is difficult to make many comparisons. All of the lipid-associated formulations achieve substantial levels in liver and splenic tissues, likely because of phagocytic uptake. Substantially higher levels of ABLC occur in the lung, but the clinical advantages of these levels have not been demonstrated. The clinical relevance of tissue concentrations of these drugs has recently been questioned, as no studies have been done to demonstrate in vivo correlates [44].

The superior safety profile of these lipid-associated formulations extends to infusion-related reactions, as well. In vitro and human clinical data demonstrate that lipid-associated formulations of amphotericin B divert signaling from a TLR-2 type reaction to a TLR-4 reaction, resulting in different responses than conventional amphotericin B, causing attenuation of the characteristic amphotericin B pro-inflammatory response [18, 45–47]. The pattern of specific cytokine production that results generally mirrors the tendency of these formulations to cause infusion-related reactions.

Within the last 20 years, three different lipid-formulated amphotericin B preparations were developed and commercially marketed. The lipid composition and molecular structure of these formulations vary considerably, causing unique pharmacokinetic profiles (Table 1). However, the impact of these unique structural and pharmacokinetic differences on specific clinical efficacy outcomes is still not proven, although it is very clear that they are much safer.

4.1 Amphotericin B Lipid Complex

ABLC (Abelcet®; The Liposome Company, Princeton, NJ, USA) received initial approval in the UK in April 1995 and was the first lipid-based formulation approved by the FDA in the USA, in December 1995. ABLC consists of amphotericin B complexed with two lipids—L-α-dimyristoyl phosphatidylcholine (DMPC) and L-α-dimyristoyl phosphatidylglycerol (DMPG); DMPC and DMPG are present in a 7:3 molar ratio with an approximate 1:1 drug to lipid ratio. These lipid-stabilized amphotericin B aggregates appear as very large ribbon-like structures with a diameter in the 1.6–11 μm range (Table 1) [7, 33–36, 40]. The DMPG component of ABLC predominately distributes into HDLs because of its interaction with the protein components, apolipoproteins A1 and AII, of the HDL particle [41].

ABLC is a relatively large compound, the largest of the lipid preparations, such that following infusion, it is recognized in blood by macrophages and is taken up rapidly in significant quantities and becomes sequestered in tissues of the mononuclear phagocyte system (e.g., liver and spleen). Consequently, compared with amphotericin B, it has lower circulating amphotericin B serum concentrations, reflected in a marked increase in V_d and clearance (Table 1). The very large V_d and correspondingly low AUC indicate rapid and extensive tissue distribution, predominately to the liver, spleen, lungs, and, to a much lesser extent, the heart, kidneys, and brain (Table 2) [7, 48]. Lung levels are considerably higher than those achieved with other lipid-associated preparations. The prolonged serum half-life is likely due to slow distribution from these tissues [49].

In addition to the decreased delivery of amphotericin B to renal tubules, as described in the previous section, it is also postulated that the enhanced therapeutic index of ABLC relative to amphotericin B is due, in part, to the relative stability of the complexes in serum along with selective release of active amphotericin B at sites of phospholipases released from activated host cells such as phagocytic cells, vascular smooth muscle cells, or capillary endothelial cells or by the fungus itself [50]. However, experiments with knock-out fungal mutants could not confirm the necessary role of fungal phospholipases in this process [51]. This postulated mechanism suggests that amphotericin B is then free to complex with the ergosterol of the fungal cell membranes to damage the organism specifically at the site of infection, rather than being released by degradation of the complex in the bloodstream, where it is more capable of contributing to toxicity.

In vitro, unlike amphotericin B deoxycholate, ABLC fails to stimulate pro-inflammatory signaling molecules TLR-2 and CD14, and either down-regulates or has no effect on macrophage pro-inflammatory cytokine gene expression [18, 20, 47]. Despite these in vitro findings, comparative clinical trials have not unequivocally demonstrated a decreased frequency of infusion-related reactions observed with this product.

4.2 Liposomal Amphotericin B

L-AmB (AmBisome®; Astellas Pharma USA, Inc. Deerfield, IL, USA) received initial approval in Ireland in 1989, but did not receive FDA approval in the USA until August 1997. It is a small unilamellar vesicle formulation, the only true liposomal preparation, and is supplied as a lyophilized powder which must be reconstituted before intravenous infusion. The liposome consists of hydrogenated soy phosphatidylcholine:cholesterol:distearoyl phosphatidylglycerol (DSPG):amphotericin B in a 2:1:0.8:1 ratio (Table 1) [7, 33, 35, 36, 40, 52, 53]. Amphotericin B is tightly bound to the liposome through charge pairing between the amino group of the amphotericin B and the phosphate group of DSPG, with further strengthening

through the interaction of the stearyl residues of the DSPG and polyene portion of the macrolide ring of amphotericin B. The multimeric barrel-pore arrangement of amphotericin B in fungal membranes is thought to be replicated in the L-AmB formulation. Each group of eight amphotericin B molecules is complexed with DSPG and cholesterol of the liposome similar to the interaction with ergosterol of the fungi [35]. Addition of cholesterol to the liposome stabilizes it against HDL destruction; consequently, <5 % of amphotericin B dissociates from the liposome during a 72-h incubation with serum [54]. Using sulphorhodamine-labeled liposomes, it has been demonstrated that L-AmB accumulates at sites of fungal infections in tissues. Gold-labeled liposomal lipid has been shown to bind to fungal membranes and penetrate into the fungal cytoplasm, suggesting that these liposomal complexes break down and release drug after contact with fungi [52, 54, 55].

Because of its small size and negative charge, the vesicle avoids substantial recognition and uptake by the mononuclear phagocyte system [32, 36, 52]. Therefore, a single dose of L-AmB results in a much higher C_{max} than conventional amphotericin B deoxycholate and a much larger AUC (Table 1). L-AmB demonstrates a similar triphasic plasma profile as amphotericin B with a very long terminal half-life of approximately 152 h [6]. Unlike amphotericin B, less than 10 % of infused drug is excreted in the urine and feces after 1 week. Total recovery of L-AmB is only 24 % compared with 93.4 % of amphotericin B; it is suspected that the drug is sequestered in deep or protected tissue compartments such as macrophages [6]. In a published dose-finding study, there was no demonstrable dose-limiting nephrotoxicity or infusion-related toxicity over a dosage range of 7.5–15.0 mg/kg/day [56]. There was a distinctly non-linear profile of plasma pharmacokinetics over the range of 7.5–15.0 mg/kg/day. C_{max} and AUC did not increase above doses of 10 mg/kg/day. Tissue concentrations in patients receiving L-AmB tend to be highest in the liver and spleen and much lower in kidneys and lung (Table 2).

In a rabbit model of hematogenous *Candida albicans* meningoencephalitis using standard dosages of amphotericin B deoxycholate and the various lipid amphotericin B preparations, significantly higher brain tissue concentrations were attained with L-AmB compared with the other lipid formulations or amphotericin B deoxycholate. Moreover, these higher levels resulted in significantly decreased fungal burden in the brain [57], supporting the role of this preparation as a preferred agent for treatment of invasive CNS fungal infections.

The small size and negative charge of the liposomes in L-AmB divert the normal macrophage response from pro-inflammatory to an anti-inflammatory cytokine profile by shifting from a TLR-2 to a TLR-4 type response [46], resulting in a decrease in the up-regulation of pro-inflammatory cytokines and attenuation of the infusion-related reactions [18, 20, 47].

4.3 Amphotericin B Colloidal Dispersion

ABCD was previously marketed as both Amphocil® and Amphotec® and was initially approved in the UK in 1994 and by the FDA in the USA in December 1996. Rights to the drug were recently acquired by Alkopharma Pharmaceuticals (Martigny, Switzerland). However, manufacturing and distribution of the drug were suspended in November 2011, and it is not yet known when or if manufacturing will resume. ABCD consists of a 1:1 molar ratio of amphotericin B and cholesteryl sulfate, a naturally occurring metabolite of cholesterol, in a highly organized structure. Two molecules of amphotericin B bind to two molecules of cholesteryl sulfate, forming a tetramer that has both a hydrophilic and a hydrophobic portion. These tetramers aggregate into spiral arms that form a disk-type structure with a diameter of approximately 122 nm and a thickness of 4 nm (Table 1) [32–35, 58].

After intravenous infusion, ABCD complexes remain largely intact and are rapidly removed from the circulation by cells of the macrophage phagocyte system, predominately by Kupfer cells of the liver, and to a lesser extent in the spleen and bone marrow (Table 2) [59]. As a result, less drug is available to bind to circulating LDLs and, consequently, less is delivered to the kidney (Table 2). On a milligram-to-milligram basis, the C_{max} achieved is lower than that attained by conventional amphotericin B, although the larger doses of ABCD that are administered produce an absolute level that is similar to amphotericin B (Table 1).

Unlike the other lipid-associated amphotericin B preparations, ABCD exhibits a general, similar trend of inflammatory gene up-regulation as that seen with conventional amphotericin B deoxycholate, resulting in increases in IL-1β, IL-1ra, MCP-1, MIP-1β, and TNFα [47]. These in vitro observations are reflected in clinical manifestations of a similar or higher frequency of infusion-related reactions with ABCD compared with amphotericin B deoxycholate. In phase I and II studies, infusion-related phenomena were frequent with ABCD. Patients receiving >4 mg/kg/day had more infusion-related reactions than those receiving ≤4 mg/kg/day. In a dose-ranging, phase I study, an increase in the daily dose to 8 mg/kg/day led to an unacceptable level of cardiovascular toxicity with hypotension [60]. Therefore, a dose of ABCD of 7.5 mg/kg/day is considered the maximum tolerated daily dose [61]. As a matter of fact, this high rate of infusion-related events led to premature discontinuation of a study comparing ABCD to fluconazole for prophylaxis of fungal

infections in neutropenic patients. Those subjects who received a dosage of 4 mg/kg/day experienced high fevers, hypotension, dyspnea, and tachypnea [62].

5 Comparative Antifungal Trials

Despite a substantial number of publications that deal with the lipid-based formulations of amphotericin B, only a limited number of well designed comparative trials have been published that describe their efficacy and safety in a systematic manner. Furthermore, only one study has been published that prospectively compared two of the lipid agents head to head, and none of the studies have compared more than two of the different formulations. In addition, there are significant heterogeneities among the studies in terms of the included formulation that was evaluated, dosages employed, syndromes examined, and study endpoints. The following discussion attempts to summarize the most important of these studies to provide some insight into the relative efficacy of these agents compared with amphotericin B and each other as well as their relative safety profiles.

5.1 Neutropenic Fever

Five major comparative trials have been published that examined the efficacy and safety of the various amphotericin B lipid preparations in the therapy of neutropenic fever. One study compared ABLC against amphotericin B deoxycholate [63]. Three of these five studies utilized L-AmB, two were comparisons against ABCD [64, 65] and one against ABLC [66], and the last study compared ABCD with conventional amphotericin B [67].

Subirà et al. [63] reported on a randomized, controlled trial that included 105 adult patients who had developed neutropenic fever after chemotherapy for either a hematological malignancy or autologous stem cell transplantation. Patients were randomly allocated to receive either ABLC at 1 mg/kg/day or amphotericin B deoxycholate at 0.6 mg/kg/day. Infusion-related adverse events occurred in 72 % of ABLC recipients and 77 % of amphotericin B recipients; this difference was not significant. Renal toxicity, defined as an increase in serum creatinine above 133 μmol/L (>1.5 mg/dL) or an increase >2 times the baseline value, was significantly less frequent in ABLC recipients at 8 versus 32 % in amphotericin B recipients ($p = 0.003$). The overall response rate was 72 % in the ABLC group compared with 48 % in the amphotericin B patients ($p = 0.018$); however, this difference was driven mainly by the higher nephrotoxicity rate in amphotericin B recipients. Overall mortality and the frequency of emergent fungal infections were no different between treatment groups.

Prentice et al. [64] reported on the results of two prospective, parallel, comparative, multicenter trials in which 338 patients were randomized to receive either conventional amphotericin B at a dose of 1 mg/kg/day or one of two different doses of L-AmB, either 1 mg/kg/day (L-AmB 1) or 3 mg/kg/day (L-AmB 3), for empirical therapy of neutropenic fever. L-AmB–treated patients had significantly fewer drug-related adverse effects, with 64 % in the amphotericin B arm, 43 % in the L-AmB 1 arm, and 36 % in the L-AmB 3 arm ($p < 0.01$). Nephrotoxicity, defined as a 100 % or greater increase in baseline creatinine, occurred in 3 % of L-AmB 3-mg patients versus 12 % of amphotericin B patients ($p < 0.01$). Hypokalemia was less frequent in both L-AmB arms ($p < 0.01$). Efficacy, which was a secondary intention-to-treat analysis, suggested better responses with L-AmB, with a 49 % response rate in the amphotericin B arm versus 58 % in the L-AmB 1 arm and 64 % in the L-AmB 3 arm ($P = 0.03$); time to defervescence was not different between treatment groups, however.

In the largest study performed with any of the lipid preparations, Walsh et al. [65] reported on a randomized, double-blind, multicenter trial that compared L-AmB and conventional amphotericin B as empirical treatment for patients with persistent fever and neutropenia. Six hundred and eighty-seven subjects were randomized 1:1 to receive either L-AmB 3.0 mg/kg/day (343 patients) or amphotericin B 0.6 mg/kg/day (344 patients). There were significantly fewer infusion-related reactions in the L-AmB arm, requiring fewer medications for treatment. The incidence of nephrotoxicity, hypokalemia, and hypomagnesemia were significantly less frequent in the L-AmB arm, as were grade 3 or 4 toxicities. Patients who received amphotericin B required more dose reductions. There were no differences in the overall success rate (50 %), survival, resolution of fever, successful treatment of baseline fungal infections, and absence of discontinuation for toxicity or lack of efficacy. There were significantly more proven fungal infections and breakthrough candidemias in the amphotericin B arm, with 27 (7.8 %) compared with L-AmB with 11 (3.2 %; $p = 0.009$). The authors concluded that the possibility of delivering the desired antifungal therapy with L-AmB may afford more sustained protection against breakthrough fungal infections.

In the only randomized study to compare lipid preparations head to head, 244 patients were enrolled into a randomized, double-blind study designed primarily to compare the safety of L-AmB at either 3 ($n = 85$) or 5 mg/kg/day ($n = 78$) with that of ABLC at 5 mg/kg/day ($n = 78$) in the empirical therapy of patients with febrile neutropenia [66]. Infusion-related events on day 1 were significantly more frequent with ABLC, occurring in 88.5 % of patients compared with 68 % in the L-AmB 3

group or 69 % in the L-AmB 5 group ($p < 0.017$). Infusion-related events that were examined included fever in 57.7 % of the ABLC group versus 23.5 % in the L-AmB 3 group and 19.8 % in the L-AmB 5 group ($p < 0.001$), and chills/rigors in 79.5 % of ABLC recipients versus 18.8 and 23.5 % in the 3 and 5 mg/kg L-AmB groups, respectively ($p < 0.001$). L-AmB at either 3 or 5 mg/kg/day had lower rates of nephrotoxicity (14.1 and 14.8 versus 42.3 %; $p < 0.01$) and toxicity-related discontinuations of therapy (12.9 and 12.3 versus 32.1 %; $p < 0.004$). Creatinine elevations in this study were modest, so some authorities have questioned the significance of these differences. No statistically significant differences were noted with respect to successful clinical response between the three groups, with 33 % of ABLC recipients responding compared with 40 and 42 % of L-AmB 3 and L-AmB 5 recipients, respectively. Overall, 61.4 % of patients failed therapy.

White et al. [67] reported on a randomized, double-blind, multicenter superiority trial in which ABCD at 4 mg/kg/day was compared with amphotericin B at 0.8 mg/kg/day for the empirical management of febrile neutropenia. Infusion-related hypoxia and chills were more common in ABCD recipients than in amphotericin B recipients ($p = 0.013$ and $p = 0.018$, respectively). Renal dysfunction was less frequent and occurred at a later time in ABCD recipients ($p < 0.001$). Therapeutic response was similar between groups, with 50 % in the ABCD group that responded compared with 43.2 % in the amphotericin B group.

5.2 Invasive Fungal Infections

Five comparative studies have been reported that describe the use of lipid preparations for treatment of invasive fungal diseases, predominately aspergillosis, in immunocompromised patients. Two of these studies incorporated ABCD [68, 69], two utilized L-AmB [70, 71], and one was a retrospective study of ABLC [72].

In one of the earliest studies to examine the efficacy of a lipid-based amphotericin B preparation in treatment of invasive fungal infections, Bowden et al. [68] reported on a double-blind, randomized, controlled trial that compared ABCD to amphotericin B. Eighty-eight patients were randomized to receive ABCD at 6 mg/kg/day, compared with 86 patients provided amphotericin B at a dose of 1–1.5 mg/kg/day. Infusion-related drug events occurred more commonly in the ABCD recipients, including chills in 53 versus 30 % ($p = 0.002$) and fever in 27 versus 16 % ($p = 0.01$). Toxicities requiring discontinuation occurred in 24 % of amphotericin B recipients and 22 % of ABCD recipients; however, eight ABCD patients required discontinuation because of infusion-related events, compared with three amphotericin B recipients. Renal toxicity was significantly more common in amphotericin B recipients at 49 versus 25 % of ABCD recipients ($p = 0.002$), and the median time to onset of renal insufficiency was 25 days in amphotericin B recipients versus 301 days in the ABCD group ($p < 0.001$). A therapeutic response occurred in 52 patients who received ABCD, compared with 51 who received amphotericin B; mortality was 36 % with ABCD and 45 % with amphotericin B, and death due to fungal infections occurred in 32 patients who received ABCD, compared with 26 in the amphotericin B group; none of these rates were significantly different. The authors concluded that ABCD had equivalent efficacy to amphotericin B and superior renal safety, but a higher incidence of infusion-related events.

White et al. [69] retrospectively compiled data from five open-label clinical trials that utilized ABCD compared with amphotericin B for therapy of invasive aspergillosis. They included patients who failed prior antifungal therapy or developed nephrotoxicity or had prior underlying renal insufficiency or developed an invasive fungal infection while receiving chemotherapy. Ultimately, 82 patients were evaluated who received ABCD at ascending doses from 2–6 mg/kg/day and 261 who received amphotericin B at doses based on clinical practice from 0.1–1.4 mg/kg/day. The groups received a similar duration of antifungal therapy. The response rate with ABCD was 48.8 %, compared with 23.4 % with amphotericin B. This difference was significantly different in favor of ABCD. For most categories of patients and sites, there were significantly better responses with ABCD (patients with hematological malignancy, pulmonary disease but not sinus disease). The mortality rate was 50 % in recipients of ABCD, compared with 71.6 % in amphotericin B recipients; this difference was significant ($p < 0.001$). The relative risk (RR) for response was 3.00 in favor of ABCD ($p = 0.002$), and the RR for mortality was 0.35 in favor of ABCD compared with amphotericin B ($p < 0.001$). Renal toxicity occurred in 8.2 % of ABCD recipients and 43.1 % of amphotericin B recipients ($p < 0.001$).

On the basis of the results of animal studies suggesting that using higher doses of L-AmB might improve efficacy [73, 74], patients with proven or probable invasive mold infections were randomized to receive L-AmB at either high or low dosages [70]. Between April 2003 and October 2004, 201 patients were enrolled from 71 sites in ten European countries and Australia. Patients were randomized to receive either 3 mg/kg/day (standard-dose group) or 10 mg/kg/day (high-dose group) for 14 days in a double-blind trial. The primary end point was favorable response (partial or complete) at the end of the 14-day study drug treatment period. Survival and safety outcomes were also evaluated. Two hundred and one patients were enrolled; 107 received 3 mg/kg/day and 94 received 10 mg/kg/day.

Ninety-seven percent of patients had invasive aspergillosis. A favorable response occurred in 50 % of patients in the standard-dose group and 46 % of the high-dose recipients; this difference was not significant. Survival rates were not different between groups at 72 % (standard dose) and 59 % (high dose). However, there were significantly higher rates of nephrotoxicity and hypokalemia in the high-dose L-AmB group. The investigators concluded that the regimen of 10 mg/kg/day demonstrated no additional benefit, but contributed to higher rates of nephrotoxicity.

Leenders et al. [71] reported on an open, randomized, comparative multicenter trial of L-AmB 5 mg/kg/day versus amphotericin B 1 mg/kg/day in the treatment of neutropenia-associated proven or probable invasive fungal infections. Responses were graded as complete, partial, or failures. Sixty-six patients were enrolled; 32 received L-AmB and 34 received conventional amphotericin B. The overall response rate in the L-AmB arm was 50 %, compared with 24 % in the amphotericin B arm; these differences were statistically significant ($p = 0.03$). In addition, the mortality rate was 22 % in the L-AmB arm, compared with 38 % in the amphotericin B arm; these differences were also significant ($p < 0.03$). No differences were detected in the mycological eradication rates. Only 1.4 % of patients in the L-AmB arm, compared with 86 % in the amphotericin B arm, had a change from baseline creatinine ($p < 0.001$). Drug discontinuations were much higher in the amphotericin B arm: 18 patients versus two patients ($p < 0.001$).

One retrospective comparison of ABLC versus L-AmB in leukemic patients with suspected and documented fungal infections has been published [72]. The overall treatment response with ABLC was 63 % (27/48), compared with 15/29 patients (39 %) treated with L-AmB ($p = 0.03$). In patients with documented fungal infections, the response rate with ABLC was 30 %, compared with 29 % with L-AmB; this difference was not significant.

5.3 Disseminated Histoplasmosis in HIV-Infected Patients

In the only comparative study performed to evaluate the efficacy of a lipid-associated product against *Histoplasma capsulatum*, Johnson et al. [75] carried out a multicenter, double-blind, prospective study for mild to moderate disseminated histoplasmosis in patients with AIDS. Seventy-three patients were randomized in a 2:1 fashion to receive either L-AmB at 3.0 mg/kg/day (51 patients) or amphotericin B at 0.7 mg/kg/day (22 patients) for a 2-week induction period. A successful clinical response was defined by the absence of fever for 72 h, stabilization of the clinical signs and symptoms, and laboratory data attributable to disseminated histoplasmosis and the resolution of at least one of the clinical criteria that qualified the patients for enrollment into the study. Clinical success at 7 days was achieved in 88 % of L-AmB recipients and 64 % of amphotericin B recipients; this difference was statistically significant ($p = 0.014$). There was no difference in median time to defervescence (3 days in each arm), fever at 14 days, blood culture clearance, or *Histoplasma* polysaccharide antigen clearance. Mortality was significantly lower in the L-AmB group, with one death (2 %) due to *Staphylococcus aureus* bacteremia compared with three deaths (13 %) due to progression of disseminated histoplasmosis in the amphotericin B group ($p = 0.04$). Infusion-related reactions were significantly more frequent with amphotericin B: 63 versus 25 % ($p = 0.002$); as was nephrotoxicity: 37 versus 9 % ($p = 0.002$). The authors concluded that for disseminated histoplasmosis in patients with AIDS, L-AmB demonstrated superior efficacy, lower toxicity, and decreased mortality.

5.4 Cryptococcal Meningitis

Three studies examined the role of lipid preparations for treatment of AIDS-associated cryptococcal meningitis, including one with ABLC [76] and two that included L-AmB [77, 78].

ABLC was tested in a randomized, open-label, ascending-dose design comparing three different dosage regimens of ABLC to a standardized regimen of amphotericin B used in consecutive patients with AIDS-associated cryptococcal meningitis [76]. Seventeen patients received amphotericin B at a dose of 0.7 mg/kg/day, and 38 patients received ascending doses of ABLC at either 1.2, 2.5, or 5 mg/kg/day. No significant differences in rates of clinical responses, mycological or overall responses were identified among the different regimens; response rates were noted to be similar to those reported in previous cryptococcal meningitis studies. Drug discontinuations occurred more frequently in amphotericin B recipients (53 %) than in ABLC recipients (24 %). There were significant differences in the number of transfusions required (18 versus 59 %; $p < 0.05$) and creatinine elevations ($p < 0.05$) in favor of ABLC. Given the small size of this study, no conclusions could be made given the relative efficacy of the two regimens, but it did demonstrate that ABLC had sufficient clinical and microbiological activity for treatment of patients with AIDS-associated cryptococcal meningitis and was significantly better tolerated than amphotericin B.

L-AmB was assessed in a treatment trial of patients with AIDS-associated cryptococcal meningitis [77]. Subjects were randomized 1:1 to receive a 3-week regimen of either L-AmB 4 mg/kg/day or amphotericin B 0.7 mg/kg/day. Twenty-eight patients were enrolled; 15 received L-AmB and 13 received conventional amphotericin B. No

difference in clinical response at 3 weeks (80 versus 86 %, respectively) was detected. The median time to clinical response was 15 days in both groups. In addition, no difference in clinical response at 10 weeks (87 versus 83 %, respectively) was identified. The microbiological response was significantly better in recipients of L-AmB at 14 days (10/15 versus 1/9; $p = 0.01$), and time to culture conversion was significantly better (7–14 days compared with >21 days). There was a 1.37-fold increase in serum creatinine in the amphotericin B recipients; this difference was significant compared with those patients who received L-AmB ($p = 0.003$).

Two different doses of L-AmB were compared with a standard dosage of amphotericin B for the treatment of AIDS-associated acute cryptococcal meningitis [78]. In this double-blind, multicenter study, patients were randomized in a 1:1:1 ratio to receive either amphotericin B at 0.7 mg/kg/day or L-AmB at either 3 or 6 mg/kg/day for an 11–21 day induction period. Repeat cerebrospinal fluid (CSF) examinations were performed at 2, 6, and 10 weeks of therapy to assess response. No differences were detected in terms of mycological response as determined by negative CSF cultures at 2 weeks (47.5, 58.3, and 48 %, respectively) or 10 weeks (78.7, 60, and 70.7 %, respectively). The clinical response rate and mortality rate at 2 and 10 weeks were similar among all arms of the study. Significantly fewer patients who received the 3 mg/kg/day dosage of L-AmB developed nephrotoxicity compared with recipients of conventional amphotericin B deoxycholate ($p = 0.004$); however, there was no difference in the development of nephrotoxicity between recipients of the higher dose L-AmB arm and conventional amphotericin B. The overall frequency of infusion-related reactions was significantly lower for both doses of L-AmB compared with conventional amphotericin B ($p < 0.001$).

6 Visceral Leishmaniasis

Pentavalent antimonials have been the standard first-line therapy for visceral leishmaniasis for decades. However, their use is complicated by toxicity, and a lack of efficacy in certain parts of the world, and they require extended durations of therapy, which contribute to increased costs. For these reasons, pentavalent antimonials do not provide a practical treatment regimen in areas of the world with limited resources. Amphotericin B has been demonstrated to have activity for therapy of visceral leishmaniasis, with a mechanism of action against *Leishmania* similar to that which exists for fungi. Unfortunately, conventional amphotericin B regimens require 15 alternate-day infusions of 1 mg/kg, making them inconvenient and expensive [79]. Based on small, non-randomized treatment studies for visceral leishmaniasis performed in the Mediterranean basin, L-AmB received FDA approval in 1999 in the USA and has more recently received approval in several other countries; moreover, a World Health Organization (WHO) working group has recommended its use for this indication [80]. Efficacy data suggested that total doses of 15–20 mg/kg were associated with very high cure rates, in excess of 95 % [81]. However, these regimens still required multiple-day dosing, and despite the availability through the WHO of preferential pricing for non-profit and public sectors in low- and some moderate-income endemic countries, the treatment costs are still substantially higher than those for pentavalent antimonials. One recently published trial, performed in India, addressed some of these issues by comparing amphotericin B deoxycholate administered as 15 alternate-day infusions of 1 mg/kg to L-AmB given as just one infusion of 10 mg/kg [82]. In this open-label study, 412 patients were ultimately randomized in a 3:1 ratio to receive either L-AmB (304 patients) or amphotericin B deoxycholate (108 patients). At day 30, the cure responses in the two groups were equivalent, with 100 % responding in the L-AmB group and 98 % in the amphotericin B deoxycholate group. At 6 months, cure rates were similar in the two groups: 95.7 % (95 % CI 93.4–97.9) in the L-AmB arm and 96.3 % (95 % CI 92.6–99.9) in the conventional amphotericin B arm. Infusion-related fevers or rigors occurred in 40 % of the L-AmB group and 64 % of the amphotericin B deoxycholate group ($p < 0.001$); increased anemia or thrombocytopenia resulted in 2 % of L-AmB recipients versus 19 % of amphotericin B deoxycholate recipients ($p < 0.001$); and hypokalemia occurred in 2 % of conventional amphotericin B recipients. Both groups had less than 1 % nephrotoxicity. Estimated treatment cost for the 30-day course of inpatient therapy associated with conventional amphotericin B was $436 (in 2010 US$) compared with $162 (in 2010 US$) for 1 day of inpatient therapy with L-AmB; if L-AmB was administered as outpatient therapy, the associated cost was $148 (in 2010 US$). The authors concluded that L-AmB was not inferior to amphotericin B deoxycholate for the treatment of visceral leishmaniasis and was less expensive.

7 Systematic Reviews

Barrett et al. [83] reported on a systematic review of the literature to compare the effectiveness and tolerability of lipid-based amphotericin formulations and conventional amphotericin B in the treatment of systemic fungal infections. The authors reviewed seven studies out of eight publications that met entry criteria regarding efficacy, mortality, renal toxicity, and infusion-related reactions.

The meta-analysis showed that lipid-based formulations significantly reduced all-cause mortality risk by an estimated 28 %, compared with conventional amphotericin B. ABCD and L-AmB significantly reduced the risk of renal dysfunction and severe adverse events. Lipid-based amphotericin B products demonstrated a significantly reduced doubling in serum creatinine compared with amphotericin B, by an estimated 58 % (odds ratio [OR] 0.42, 95 % CI 0.33–0.54), yielding a number needed to treat of six (i.e., for every six treated, one will be prevented from having a doubling of his serum creatinine). There was also a trend towards a reduction in infusion-related reactions among recipients of lipid-based amphotericin B products (OR 0.79, 95 % CI 0.58–1.08).

In a Cochrane review that was performed in order to compare the benefits and harms of lipid formulations of amphotericin B with conventional amphotericin B in cancer patients with febrile neutropenia, 12 studies were reviewed [84]. Six of these studies, however, utilized preparations of amphotericin B given along with Intralipid®. These authors concluded that (1) lipid-based amphotericin B preparations were not more efficacious than conventional amphotericin B for mortality (RR 0.83, 95 % CI 0.62–1.12); (2) lipid-based amphotericin B formulations were associated with fewer invasive fungal infections (RR 0.65, 95 % CI 0.44–0.97); (3) lipid-based amphotericin B formulations were associated with a decreased risk of nephrotoxicity (RR 0.45, 95 % CI 0.37–0.54); and (4) lipid-based amphotericin B preparations were associated with fewer treatment drop-outs (RR 0.78, 95 % CI 0.62–0.97), suggesting that they were better tolerated.

Another review and meta-analysis, by Girois et al. [85], published in 2006, examined the adverse effects of the major systemic antifungal therapies. The authors reviewed 54 studies, which included 9,228 patients, and assessed them for the frequency of various adverse events. These authors emphasized the marked heterogeneity among patients included in the various trials, the incomplete reporting of adverse events, and the inconsistent definitions that were utilized. Furthermore, the authors noted that they encountered difficulties combining data sets because of the range of criteria and methods (e.g., direct observations) used to define drug-related adverse events. Consequently, rates for the various drug-related adverse events ranged widely and made direct comparisons difficult. Regardless, some conclusions were able to be derived from the data. Infusion-related acute drug reactions, specifically fever, occurred in 34.2 % of 1,180 patients receiving amphotericin B, 31.1 % of 386 patients who received ABLC, 37.2 % of 816 ABCD recipients, and 11.2 % of 1,126 L-AmB recipients. For nephrotoxicity, it was clear that conventional amphotericin B was the most nephrotoxic agent. Of 1,850 patients assessed, 33.2 % (95 % CI 30.8–36) developed nephrotoxicity, resulting in discontinuation of the drug in 4.8 % (95 % CI 4.3–6.3). For ABCD, the rate of nephrotoxicity among 456 patients was 21.1 % (95 % CI 17.2–26.2), causing discontinuation of the drug in only 0.3 % of patients (95 % CI 0.3–1.6). ABCD caused nephrotoxicity in 16.5 % (95 % CI 14.8–18.3) of 3,067 patients, resulting in its discontinuation in 1 % (95 % CI 0.8–1.8) of recipients. L-AmB caused nephrotoxicity in 14.6 % (95 % CI 12.4–17.5) of 1,554 patients, resulting in discontinuation in 0.3 % (95 % CI 0.3–1.6). Rates of hepatotoxicity were similar among the four preparations, between 14.1–16 %, and necessitated discontinuation of drugs in less than 1 %.

In a recent review and meta-analysis that compared the drug-induced nephrotoxicity associated with either ABLC or L-AmB, Safdar et al. [86] identified 11 studies that were reported between 1995 and 2008 that compared nephrotoxicity resulting from the use of the two agents. Three studies were excluded because of a lack of comparison groups, incomplete data, or inclusion of a neonatal population. The results of the analysis of the remaining eight studies showed an increased probability of nephrotoxicity in patients who were treated with ABLC as compared with L-AmB (OR 1.75, RR 1.55). However, there was considerable heterogeneity among the studies and the results were heavily influenced by an inordinately high and unexplained rate of nephrotoxicity cited in one particular study [66]. When that study was removed from the analysis, the risk of nephrotoxicity was more similar between the two preparations (OR 1.12, RR 1.09). The authors concluded that nephrotoxicity was "generally similar for ABLC and L-AmB in patients receiving antifungal therapy and prophylaxis" [86].

8 Conclusions

Despite its unfavorable safety profile, some form of amphotericin B still represents the best proven and most important therapeutic option for treatment of invasive fungal infections in salvage situations as well as in the management of breakthrough fungal infections in compromised patients. Unfortunately, use of amphotericin B is seriously complicated by dose-related toxicities such as infusion-related reactions and the development of nephrotoxicity. In an attempt to attenuate the substantial toxicity associated with infusions of amphotericin B deoxycholate, three commercial amphotericin B lipid formulations were developed. These drugs have considerable compositional and structural differences that result in distinctive pharmacokinetic profiles. However, despite these differences, there is not any clear published evidence of a correlation between these pharmacokinetic profiles and different

clinical outcomes. Although these drugs have now been available for almost 20 years, there is a paucity of well designed, randomized trials designed to compare these agents in different clinical settings. Those trials that have been performed suffer from considerable heterogeneity in the diseases studied, drugs chosen for study, dosages utilized, definitions of responses, and outcomes evaluated. Nevertheless, some conclusions regarding the relative efficacy and safety of the lipid-based formulations can be derived from the available data.

For empiric therapy in febrile neutropenic patients, all of the lipid-based formulations are significantly better in preventing breakthrough invasive fungal infections when compared with amphotericin B. Furthermore, there is probably a modest improvement in mortality compared with conventional amphotericin B deoxycholate.

For invasive fungal infections, particularly aspergillosis, a favorable therapeutic response to lipid-based amphotericin B preparations can be expected in 40–60 % of patients after approximately 2–3 weeks of therapy. The results of one meta-analysis determined that the lipid-based formulations reduced all-cause mortality by 28 % compared with amphotericin B deoxycholate. However, there were no particular benefits from administering higher doses of lipid-based preparations (e.g., 10 mg/kg/day) compared with standard dose regimens (e.g., 1–3 mg/kg/day); this was specifically studied with L-AmB.

L-AmB did demonstrate superior efficacy and a mortality benefit for the treatment of disseminated histoplasmosis in patients with HIV infection compared with conventional amphotericin B deoxycholate, although L-AmB did not provide an improvement in any microbiological endpoints. For the treatment of AIDS-associated acute cryptococcal meningitis, the lipid-associated formulations do not appear to offer any therapeutic, microbiological, or mortality benefit compared with amphotericin B deoxycholate, nor were there any differences between higher doses (6 mg/kg/day) and lower doses (3 mg/kg/day) of L-AmB in any outcomes studied.

All of the lipid-associated amphotericin B formulations clearly provide a safer alternative than conventional amphotericin B for any clinical syndromes that have been investigated, especially for the kidneys, where they result in significantly less nephrotoxicity. There appears to be a trend towards fewer infusion-related reactions, especially for L-AmB, and possibly ABLC. However, ABCD has a similar or higher frequency of infusion-related reactions compared with conventional amphotericin B deoxycholate. This high frequency of infusion-related reactions resulted in discontinuation of a least one clinical trial, has resulted in its infrequent clinical use, and is likely partially responsible for the removal of this preparation from the commercial market.

Until newer drugs are developed that have improved antifungal activity, better pharmacokinetics and modes of delivery, and improved safety profiles, clinicians will need to depend on some form of amphotericin B for the treatment of some problematic fungal infections in compromised patient populations. There do not appear to be major efficacy differences between the two commercial preparations presently available, ABLC and L-AmB. Evidence suggests that L-AmB may be marginally safer, but the differences are not significant. As the price of these agents continues to decrease, it is likely that they will retain their utility in the present antifungal armamentarium.

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