Amphotericin B: Time for a New "Gold Standard"

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When introduced in 1959, amphotericin B deoxycholate (AmBD) was clearly a life-saving drug. Randomized studies demonstrating its efficacy were not thought to be necessary, and it was granted indications for many invasive fungal infections. Despite its formidable toxicities, AmBD is thus often used as the primary comparator in studies of invasive fungal infections. Safer lipid-based versions of amphotericin B (AmB) have been introduced, but difficulties with studying these agents generally led to licensure for salvage therapy, not primary therapy. However, the cumulative clinical experience to date with the lipid-based preparations is now adequate to demonstrate that these agents are no less active than AmBD, and, for some infections, it can now be stated that specific lipid-based preparations of AmB are superior to AmBD. Given their superior safety profiles, these preparations can now be considered suitable replacements for AmBD for primary therapy for many invasive fungal infections in clinical practice and research.

More than 40 years of clinical experience have proven that amphotericin B deoxycholate (AmBD) is a reliable antifungal agent. These 40 years of experience have also proven that AmBD is a toxic compound. For most of this time, clinicians had few other therapeutic options, and they thus created complex and sometimes even mystical procedures to minimize the acute and chronic toxicities of AmBD. But new therapeutic options now offer an escape from this bind. The new choices include improved azole antifungal agents, the novel class of echinocandin antifungal agents, and the less toxic lipid formulations of amphotericin B (LFABs; table 1). These agents have proven their value in a variety of clinical and research settings in far more systematic studies than were ever conducted for AmBD.

Despite these advances, AmBD is still frequently used in medical therapy and clinical trials because of its broad range of licensed indications—it is the only antifungal with an indication for initial therapy for many fungal infections and is often thought to be the "gold standard" for therapy. However, and for reasons that we will discuss, we think it is time to pass the gold standard torch to its contemporary counterparts. We present evidence to prove that LFABs can now be accepted as replacements for AmBD for both routine clinical use as well as for clinical investigation of new antifungal agents. The argument in favor of this position will be made both on the basis of data supporting efficacy at least equal to that of AmBD and, perhaps even more importantly, on the basis of the association of the lesser toxicities of LFABs with clinical benefit.

HISTORICAL PERSPECTIVE

The first antifungal agent developed for the treatment of invasive mycoses was nystatin; however, its development as a systemic agent was thwarted by severe toxicities [1]. AmBD was licensed in 1959 on the basis of open-label, noncomparative data [2], and its current package insert states that it is licensed for the treatment of "progressive and potentially life threatening fungal infections: aspergillosis, cryptococcosis (torulosis), North American blastomycosis, systemic candidiasis, histoplasmosis, zygomycosis including mucormycosis due to susceptible species of the genera *Absidia, Mucor* and *Rhizopus,* and infections due to related susceptible species of *Conidiobolus* and *Basidiobolus,* and sporotrichosis" [3]. Although some studies have shown high rates of failure of AmBD for certain conditions [4, 5], there is little question about its overall efficacy. However, the toxicities associated

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Table 1. US Food and Drug Administration–approved lipid-based formulations of amphotericin B (AmB) and their indications and dosages.

Name	Approved indication	Approved dosage
AmB lipid complex (Abelcet, Enzon Pharmaceuticals)	Treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional AmB therapy	5 mg/kg q.d.
Liposomal AmB (AmBisome, Gilead Sciences)	Empirical therapy for presumed fungal infection in febrile, neutropenic patients; treatment of cryptococcal meningitis in HIV-infected patients; treatment of patients with *Aspergillus, Candida,* and/or *Cryptococcus* infections refractory to AmB deoxycholate, or in patients in whom renal impairment or unacceptable toxicity precludes the use of AmB deoxycholate; and treatment of visceral leishmaniasis	3 mg/kg q.d. for empirical therapy, 3–5 mg/kg q.d. for systemic fungal infections, and 6 mg/kg q.d. for cryptococcal meningitis in HIV-infected patients
AmB cholesteryl sulfate complex (Amphotec, Intermune Pharmaceuticals)	Treatment of invasive aspergillosis in patients in whom renal impairment or unacceptable toxicity precludes the use of AmB deoxycholate in effective doses, and in patients with aspergillosis for whom previous AmB deoxycholate therapy has failed	3–4 mg/kg q.d.

with AmBD are such that one might speculate whether, under current approval criteria, AmBD would meet requirements for licensing. Toxicity issues may influence outcomes because need for dose reduction often precludes adequate dosing and thus leads to progressive infection and therapeutic failure.

Although other agents have been subsequently introduced, AmBD has remained the treatment of choice for many life-threatening fungal infections in vulnerable hosts because of both its spectrum of activity and its low rates of resistance [6, 7]. The development of lipid-based delivery technologies offered the possibility of reduced toxicity and resulted in the birth of the 3 LFABs: amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD), and liposomal amphotericin B (LAmB) [8, 9]. As summarized in table 1, these agents are currently licensed for the treatment of invasive fungal infections in patients refractory to or intolerant of AmBD. In addition, LAmB is licensed for use in the patients with neutropenia who have fever and presumed fungal infection, as well as visceral leishmaniasis. Although the licensing decisions in the United States for these compounds were based primarily on data from open-label, noncomparative studies [10], there is now a large body of data that supports the efficacy and safety of these compounds in the primary treatment of systemic fungal infections.

DATA SUPPORTING SUPERIOR SAFETY WITH AT LEAST EQUIVALENT EFFICACY FOR LFABs WITH RESPECT TO AmBD

Support for the utility of LFABs might be sought from in vitro susceptibility data, from results of in vivo models, and from results of studies involving humans. Of these data, the most valuable are the in vivo models and the studies involving humans.

In vitro evidence. Susceptibility testing of *Candida* species, *Cryptococcus neoformans,* and several different moulds by means of modified NCCLS broth microdilution methodology has generally shown higher MICs and minimum fungicidal concentrations for all LFABs [11, 12]. The rank order for in vitro activity tends to be AmBD, followed by ABLC, then ABCD, then LAmB. However, the in vitro evaluation of the activity of LFABs with respect to AmBD is confused by differences in drug release created by the lipid carrier. The role of the lipid wrapper is to change in vivo drug delivery, not to provide optimal in vitro drug release. Thus, the in vitro differences among the compounds are of uncertain relevance. Because in vitro resistance to the parent amphotericin B (AmB) compound has been shown to translate in to in vivo resistance to LFABs [13], most investigators have focused on in vivo evaluations of efficacy and potency. Further research is needed to determine the optimal way to evaluate in vitro susceptibility, especially as LFABs are used more frequently.

In vivo evidence. Relative to AmBD, murine and rabbit models have demonstrated that a higher dose of LFAB is sometimes needed to clear *Candida, Cryptococcus,* and mould infections [13–15]. However, these higher doses are well tolerated and produce better outcomes than maximal tolerated doses of AmBD. In an especially instructive example, Clark et al. [14] compared ABLC and AmBD in a rat model of invasive aspergillosis (table 2). At a low inoculum (10^5 conidia), both AmBD and ABLC were efficacious, but the equipotent dose of ABLC was found to be 5 times higher than that of AmBD. At a higher inoculum (10^6 conidia), the toxicity of AmBD was such that an effective dose could not be administered. On the other hand,

Table 2. Toxicity and efficacy comparison of amphotericin B lipid complex (ABLC) versus amphotericin B deoxycholate (AmBD).

	ED_{50} in mg/kg per day, by inoculum	
Agent	10^5 conidia	10^6 conidia
AmBD	0.5	>0.8
ABLC	2.3	4.1

NOTE. Shown is the estimate of ED_{50} for prolongation of survival in a corticosteroid-immunosuppressed rat model of aspergillosis [14]. Rats were infected intravenously with the stated inoculum of *Aspergillus fumigatus* conidia. Therapy began 5 h after dosing and continued for 7 days. The ED_{50} at 10^6 conidia could not be estimated for AmBD because of the toxic side effects of AmBD administration. ABLC was provided at doses as high as 12.8 mg/kg without evidence of toxic manifestations.

the increased dose of ABLC required to overcome this higher inoculum was tolerated without toxic manifestations.

Similar supporting data have been reported for LAmB in a neutropenic rabbit model [16] and provide further insights into the value of LFABs. In this model, invasive pulmonary aspergillosis was initiated in persistently neutropenic rabbits, and antifungal therapy was initiated 24 h later. When AmBD and LAmB were compared, LAmB was not only statistically more effective than AmBD, but it was also less nephrotoxic (figure 1). Efficacy was maximized and toxicity was minimized at 5 mg/kg of LAmB per day.

Pharmacokinetics and pharmacodynamics are another avenue toward understanding of relative drug activities [17], but the pharmacokinetics of AmBD and LFABs are incompletely understood [6, 18, 19], and the available data do not provide strong insights. Peak serum concentrations of AmB after administration of AmBD are 1.5–2.0 mg/L, and the drug is widely distributed. The organs with the highest concentrations are liver, kidney, and lung, but the ultimate fate of the drug is unknown [6]. LFABs, in contrast, show a range of peak serum AmB concentrations. ABLC and ABCD show peak AmB concentrations similar to those for AmBD, whereas LAmB shows higher peak concentrations (10–35 mg/L) [19–21]. Tissue concentrations, on the other hand, do not follow those in the serum (table 3), with LAmB producing tissue AmB concentrations in liver, spleen, lung, and kidney that are generally lower than those produced by the other LFABs. An exception to this rule may be in the brain, where LAmB achieves higher concentrations [25].

Although other factors also affect toxicity, the lower tissue AmB levels in the kidney seen with all 3 LFABs in comparison to those seen with AmBD may account in part for their lesser degrees of nephrotoxicity. The pharmacokinetics of these drugs are further affected by the physicochemical properties of their lipid base, but they are all concentrated in the reticuloendothelial system. This particular feature is thought to be an advantage because it may promote more effective delivery of the drug to infection sites, although this has not been clearly demonstrated. It has recently been shown that the pharmacodynamic parameter that best correlated with outcome for AmBD is peak serum level/MIC of the organism [26], but it is not at all clear how this idea would translate to LFABs.

Clinical evidence. Although valuable as indications of drug activity, animal models do not completely reflect the situation seen in humans. The available open-label data and the studies comparing AmBD with LFABs are summarized in tables 4–6, and these data are discussed in the following sections.

Overview of safety issues. A principal advantage of LFABs is their superior safety with respect to AmBD. Adverse events and toxicities associated with AmBD use can be classified in 2 categories: (1) acute or infusion-related toxicities, and (2) chronic or cumulative dose-related toxicities. The infusion-related toxicities are nausea, vomiting, fever, chills, rigors, thrombophlebitis, headache, arthralgias, myalgias, bronchospasm, hypotension, and arrhythmias [6]. Dose-related toxicities correlate with end organ concentration and damage. These include potassium and magnesium wasting, anemia, and renal failure [6]. Prevention and management of these complications involves intensive hydration along with time- and resource-consuming electrolyte monitoring and replacement [44, 45].

Importantly, the impact of AmBD nephrotoxicity appears to have been underestimated. A recent study [46] showed an incidence of acute renal failure of 30% among general hospital patients treated with AmBD, with a corresponding increase in the mortality rate, length of hospital stay, and an estimated additional cost of nearly $30,000 per episode. A previous study of patients receiving AmBD for treatment of invasive aspergillosis found qualitatively similar results [47]. The costs of treatment of AmBD-induced toxicities are sufficiently large that a pharmacoeconomic analysis suggested that a less nephrotoxic LFAB would be cost-effective in some settings, even when priced much higher than AmBD [48]. Moreover, there may be important clinical outcomes associated with cumulative nephrotoxicity, even when acute renal failure does not develop, because even slightly impaired renal function can complicate the management of intercurrent illnesses.

Despite these advantages, it is important to realize that LFABs are not free of toxicities, and in fact they can be as severe as those of AmBD. In addition to similar infusion-related reactions, patients can also experience renal failure, liver toxicity, and severe hypersensitivity reactions, which may be even exacerbated when switching from one LFAB to another [49, 50]. However, as discussed in the following sections, these toxicities consistently appear less frequent, less intense, or both when compared with those associated with AmBD.

Open-label studies. Because few comparative studies have been performed, open-label studies are a major source of data on the efficacy of these compounds in proven invasive fungal

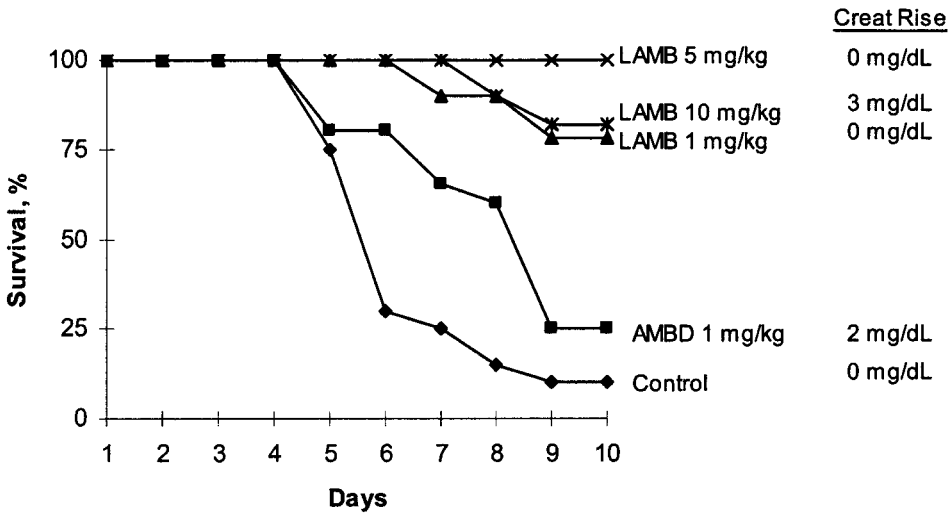

Figure 1. Comparison of toxicity and efficacy of liposomal amphotericin B (LAMB) and amphotericin B deoxycholate (AMBD). Survival in the neutropenic rabbit model of invasive pulmonary aspergillosis is shown [16], along with an increase in the creatinine level from the beginning to the end of the experiment. All LAMB groups had a survival rate that was superior ($P < .01$) to the AMBD and control groups. Data adapted from [16]; used with permission from the University of Chicago Press. Creat Rise, increase in creatinine level.

infections. When we searched the literature, we found 8 open-label studies containing data from which we could extract efficacy rates for proven disease (table 4). In addition, there is a retrospective study [51] that compares ABLC and LAmB and shows good efficacy rates for both, but absolute differential success rates by disease cannot be extracted. These studies all used diagnostic criteria similar to the proven category of the recently published EORTC-MSG criteria for the diagnosis of invasive fungal infections [52]. These studies include a mix of pediatric and adult populations. The patients were generally immunocompromised and had infections that were refractory to standard therapy, or the patients were unable to tolerate standard therapy. In general, the previous therapy received had been AmBD. Although we recognize the potential for variation between studies, aggregate efficacy estimates from these data were compiled and are shown in table 5. Also provided are comparable efficacy rates for AmBD from large clinical trials. In each case, the aggregate rate for LFABs is quite similar to the rate for AmBD. In general, ABLC and LAmB appeared to have better success rates than does ABCD.

Controlled studies. Table 6 summarizes the 10 major controlled studies reported to date that compare AmBD with an LFAB. All studies are randomized, prospective studies. Of these studies, 6 were blinded [36–38, 42, 43, 57, 58], 5 were performed for a defined fungal infection [40–42, 57, 58], and 4 were studies of empirical therapy for persistent fever in patients with neutropenia [35–38]. As is easily seen from table 6, toxicity monitoring in these trials found a clear, definite, and consistent advantage for LFABs. Although infusion-related events were still present in some trials, renal toxicity was dramatically reduced.

All trials showed at the very least similar efficacy for LFABs, compared with AmBD, in terms of response and survival parameters. Some trials even demonstrated specific advantages, such as faster culture conversion in cryptococcal meningitis [41]. Of these studies, perhaps the most instructive is the study reported by Walsh et al. [37] of a randomized, double-blinded, multicenter trial comparing LAmB with AmBD as therapy of fever and neutropenia in patients with cancer. In this study, LAmB was compared with AmBD in 687 patients. The 2 drugs showed similar global efficacy, but LAmB was clearly safer. Patients randomized to receive LAmB had fewer infusion-related fever reactions (17% vs. 44%), less-frequent chills or rigors (18% vs. 54%), and fewer miscellaneous reactions (e.g., hypotension and hypoxia). Increase in serum creatinine level to more than

Table 3. Relative tissue concentrations of amphotericin B after administration of the lipid formulations of amphotericin B (AmB).

	Tissue concentration		
Organ	ABCD	ABLC	LAmB
Liver	2×	2×	0.5–1×
Spleen	0.4×	5×	3×
Lung	NA	2×	0.2×
Kidney	0.1×	0.2×	0.2×
Brain	0.1×	0.2×	1.2×

NOTE. Shown are the tissue concentrations of lipid formulations of AmB after 1 mg/kg of each lipid formulation of AmB relative to the concentration achieved following 1 mg/kg AmB deoxycholate. The data were adapted from rat, murine, and rabbit data [14, 22–25]. ABCD, amphotericin B colloidal dispersion; ABLC, AmB lipid complex; LAmB, liposomal AmB; NA, not applicable.

Table 4. Major open-label clinical studies assessing the safety and efficacy of lipid formulations of amphotericin B for invasive fungal infections.

Study	Year	No. of subjects	Product	Study population	Organisms	Response	Adverse event
Mehta et al. [27]	1997	64	ABLC	Patients with hematological conditions, transplant recipients	*Candida, Aspergillus,* and *Cryptococcus* species	10 of 14 with confirmed IFI; 24 of 39 with suspected IFI	SCr level doubled in 7 patients; 4 patients discontinued therapy
Walsh et al. [28]	1998	556	ABLC	Patients with hematological conditions, transplant recipients, patients with AIDS	*Candida, Aspergillus Cryptococcus, Mucor, Fusarium* and other species	167 of 291 assessable cases	SCr level either improved or was unchanged
Walsh et al. [29]	1999	111	ABLC	Pediatric patients with fungal infections	*Candida, Aspergillus, Mucor, Fusarium,* and other species	38 of 54 assessable cases	No significant changes in renal function; increase in bilirubin levels
Oppenheim et al. [30]	1995	168	ABCD	Patients with hematological conditions, transplant recipients, patients with AIDS	*Candida, Aspergillus Cryptococcus, Mucor, Fusarium,*and other species	19 of 33 *Candida,*11 of 32 *Aspergillus,* 5 of 11 *Cryptococcus,* 4 of 4 zygomycoses, 1 of 4 *Fusarium*	Minimum renal toxicity, hypokalemia in 8 of 168 patients
Mills et al. [31]	1994	116	LAm B	Patients with hematological conditions, transplant recipients	*Candida* and *Aspergillus* species	13 of 17 with confirmed aspergillosis	Acute reactions in 5 patients; hepatic dysfunction in 23 patients; and hypernatremia in 17 patients; no significant renal impairment noted
Ng et al. [32]	1995	58	LAmB	Patients with hematological conditions	*Aspergillus, Candida,* and other species	10 of 17 *Aspergillus,* 5 of 9 *Candida*	2 patients had minimal increase in the SCr level
Tollemar et al. [33]	1992	59	LAmB	Patients with hematological conditions, transplant recipients, patients with other immunodeficiencies	*Candida, Aspergillus,* and other species	30 of 36 *Candida,* 11 of 18 *Aspergillus*	SCr level increase in 9 patients; pancreatitis in 1
Ringden et al. [34]	1991	126	LAmB	Patients with hematological conditions, transplant recipients, patients with AIDS, patients with other immunodeficiencies	*Aspergillus, Candida,* and other species	17 of 28 *Aspergillus,* 21 of 25 *Candida,* 11 of 11 others	Minimal—not described in detail

NOTE. ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; IFI, invasive fungal infection; LAmB, liposomal amphotericin B; SCr, serum creatinine.

Table 5. Aggregate efficacy estimates for amphotericin B formulations from open-label studies.

	ABCD		ABLC		LamB		All LFABs		AmBD reference rate	
Disease	*n*/*N*[a]	Complete and partial responses, % (95% CI)	*n*/*N*[a]	Complete and partial responses, % (95% CI)	*n*/*N*[a]	Complete and partial responses, % (95% CI)	*n*/*N*[a]	Complete and partial responses, % (95% CI)	*n*/*N*[a]	Complete and partial responses, % (95% CI)
Aspergillosis	11/32	34 (19–53)	75/163	46 (38–54)	51/84	61 (49–71)	137/279	49 (43–55)	42/133	32 (24–40)
Candidiasis	19/33	59 (39–75)	92/123	75 (66–82)	56/70	80 (69–89)	167/226	74 (68–79)	81/103	79 (69–86)
Cryptococcosis	5/11	45 (17–77)	8/12	67 (35–90)	1/1	100 (2–100)	14/24	58 (37–78)	11/27 HIV-uninfected subjects 25/63 HIV-infected subjects	41 (22–61) HIV-uninfected subjects 40 (26–53) HIV-infected subjects
Fusariosis	1/4	25 (1–81)	10/12	83 (52–98)	—	—	11/16	69 (41–89)	—	—
Phaeohyphomycosis	—	—	1/5	20 (1–72)	—	—	1/5	20 (1–72)	—	—
Zygomycosis	4/4	100 (40–100)	18/25	72 (51–88)	1/1	100 (2–100)	23/30	77 (58–90)	—	—
Mixed Infections	3/6	50 (12–88)	—	—	—	—	3/6	50 (12–88)	—	—
Other	5/7	71 (29–96)	11/15	73 (45–92)	14/14	100 (77–100)	30/36	83 (67–94)	—	—

NOTE. Data on efficacy for proven invasive fungal infections were extracted from the studies summarized in table 4. The AmBD reference rates are from Herbrecht at al. [53] for aspergillosis, Rex et al. [54] for candidiasis, Bennett et al. [55] for cryptococcosis in HIV-uninfected individuals, and Saag et al. [56] for cryptococcosis in HIV-infected individuals. ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; AmBD, amphotericin B deoxycholate; LAmB, liposomal amphotericin B; LFAB, lipid formulations of amphotericin B.

[a] No. of complete and partial responses/no. of patients treated. Success is not defined uniformly in the studies but always includes a combination of clinical and microbiological response elements.

Table 6. Major controlled clinical trials assessing the safety and efficacy of lipid formulations of amphotericin B (AmB).

Study	Year	Study design	No. of subjects	Drugs (doses) compared	Patient symptoms or conditions	Organism	Global response[a]		Adverse events
							Success rate, %	*P*	
Prentice et al. [35]	1997	Randomized, prospective	134 adults, 204 children	LAmB (1 mg/kg) vs. LAmB (3 mg/kg) vs. AmBD (1 mg/kg)	Neutropenia and fever	—	58% for LAmB 1 mg/kg vs. 64% for LAmB 3 mg/kg vs. 49% for AmBD	.03	Renal toxicity (defined as 100% increase from baseline SCr level), 0% for LAmB 1 mg/kg vs. 3% for LAmB 3 mg/kg vs. 12% for AmBD
White et al. [36]	1998	Randomized, double-blind, prospective	213	ABCD (4 mg/kg) vs. AmBD (0.8 mg/kg)	Neutropenia and fever	—	50% for ABCD vs. 43% for AmBD	—	Renal toxicity (defined as 100% increase from baseline SCr level), 0% for ABCD vs. 54% for AmBD; if defined as 50% decrease in creatinine clearance, 43% for ABCD vs. 100% AmBD; infusion-related events (hypoxia and chills) occurred in 13 patients receiving ABCD vs. 3 receiving AmBD[b]
Walsh et al. [37]	1999	Randomized, double-blind, prospective	687	LAmB (3 mg/kg) vs. AmBD (0.6 mg/kg)	Neutropenia and fever	—	50% for LAmB vs. 49% for AmBD; for breakthrough fungal infections, 3% for LAmB vs. 8% for AmBD	.009	Renal toxicity (defined as 100% increase from baseline SCr level), 19% for LAmB vs. 34% for AmBD; fewer infusion-related reactions with LAmB (17% vs. 44%)
Wingard et al. [38]	2000	Randomized, double-blind, prospective	244	LAmB (3 mg/kg) and (5 mg/kg) vs. ABLC (5 mg/kg)	Neutropenia and fever	—	40% for LAmB 3 mg/kg vs. 42% for LAmB 5 mg/kg vs. 33% for ABLC	—	Renal toxicity (defined as 100% increase from baseline SCr level), 14% for LAmB 3 mg/kg vs. 15% for LAmB 5 mg/kg vs. 24% for ABLC
Leenders et al. [39]	1998	Randomized, prospective	66	LAmB (5 mg/kg) vs. AmBD (1 mg/kg)	Neutropenia with suspected or documented fungal infection	*Candida* and *Aspergillus* species and other moulds	50% for LAmB vs. 24% for AmBD	.04	Renal toxicity (defined as 100% increase in SCr level), 19% for LAmB vs. 64% for AmBD
Ellis et al. [40]	1998	Randomized, prospective	87	LAmB (1 mg/kg) vs. LAmB (4 mg/kg)	Neutropenia with suspected aspergillosis	*Aspergillus* species	64% for LAmB 1 mg/kg vs. 48% for LAmB 4 mg/kg	—	Renal toxicity (not defined), 11% for LAmB 4 mg/kg vs. 2% for LAmB 1 mg/kg
Leenders et al. [41]	1997	Randomized, prospective	28	LAmB (4 mg/kg) vs. AmBD (0.7 mg/kg)	AIDS and cryptococcosis	*Cryptococcus* species	80% for LAmB vs. 86% for AmBD[c]	<.05	No differences in adverse events
Hamill et al. [42]	1999	Randomized, double-blind, prospective	267	LAmB (3 mg/kg) vs. LAmB (6 mg/kg) vs. AmBD (0.7 mg/kg)	AIDS and cryptococcosis	*Cryptococcus* species	66% for LAmB 3 mg/kg vs. 75% for LAmB 6 mg/kg vs. 66% for AmBD	—	Renal toxicity (defined as 100% increase in SCr level), 14% for LAmB 3 mg/kg vs. 21% for LAmB 6 mg/kg vs. 33% for AmBD
Johnson et al. [58]	2002	Randomized, double-blind, prospective	81	LAmB (3 mg/kg) vs. AmBD (0.7 mg/kg)	AIDS and histoplasmosis	*Histoplasma capsulatum*	89% for LAmB vs. 59% for AmBD	.01	Renal toxicity (defined as 100% increase in SCr level), 9% for LAmB vs. 53% for AmBD
Bowden et al. [57]	2002	Randomized, double-blind, prospective	174	ABCD (6 mg/kg) vs. AmBD (1.0–1.5 mg/kg)	Invasive aspergillosis	*Aspergillus* species	35% for ABCD vs. 35% for AmBD	—	Renal toxicity (defined as 100% increase in SCr level), 12% for ABCD vs. 38% for AmBD

NOTE. ABCD, amphotericin B colloidal dispersion; AmB, amphotericin B; AmBD, AmB deoxycholate; LAmB, liposomal AmB; SCr, serum creatinine.

[a] Except as noted, response comparisons were not statistically different between arms. Success is not defined uniformly in the studies but always includes a combination of clinical and microbiological response elements.

[b] Although similar numbers of patients were enrolled onto the 2 arms of the study via a 1:1 randomization, it is not possible to precisely determine the denominator for these events from the published report; the difference is said to have $P = .013$.

[c] Median time to sterile CSF culture was <14 days for LAmB recipients and >21 days for AmBD recipients.

double the upper limit of normal occurred in 19% of subjects provided LAmB and 34% of those provided AmBD ($P < .001$). In addition, LAmB also showed evidence of superior microbiological activity with fewer breakthrough fungal infections on LAmB (3.2%), compared with AmBD (7.8%; $P = .009$).

Some of the trials in this area also compare LFABs either with themselves at different dosages [35] or with each other [38]. Although strong data regarding the most efficacious LFABs (or doses of LFABs) are not available, LAmB appears to have relative advantages over the other products with respect to nephrotoxicity.

THE CHALLENGE OF CLINICAL TRIALS FOR DRUG REGISTRATION

As a related but distinct issue, the question of adoption of LFABs as a standard approach has a special implication in the context of clinical trials and drug registration. Although clinical trials can take many forms, a state-of-the-art therapeutic clinical trial for a new anti-infective agent generally requires that the new drug or intervention in question be compared in a randomized and blinded fashion with an agent that is already licensed for treatment of the infection under study. Ideally, this will clearly assess whether the new intervention offers either efficacy or safety advantages over the comparator. Placebo-controlled trials are generally not suitable in this area. In addition, it is often thought desirable to have results available from ≥ 2 independently conducted studies.

Meeting these challenges with antifungal agents is difficult both because of the limited number of patients with mycoses that can be readily studied and because of the paucity of suitable comparative agents [10]. Even though mycoses are clearly a major and growing cause of morbidity and mortality [59–61], the lack of adequate diagnostic tools makes timely diagnosis difficult. Further compounding this difficulty is the fact that AmBD is the only agent licensed as initial therapy for many mycoses. At the time of its licensure in 1959 [2], AmBD's open-label activity against a variety of mycoses was sufficiently striking that its acceptance was prompt and durable. To date, AmBD remains the agent with the broadest spectrum of action and the least potential for resistance of any known antifungal agent [62]. Despite its formidable toxicity, both clinical investigators and regulatory agencies have thus long thought that AmBD was the most suitable comparator for many trials of antifungal agents. However, AmBD's toxicity also limits its acceptance by the patient and clinicians, and the increasing availability of alternative antifungal agents makes patient enrollment onto and retention in clinical trials very difficult.

The availability of less toxic LFABs has begun to change this equation. Because these agents were not licensed on the basis of head-to-head comparisons with AmBD [10], there was initially some reluctance to use them as substitutes for AmBD in clinical trials. Concerns over differences in pharmacokinetics and tissue delivery have been mentioned as reasons to continue to rely upon the classical AmBD formulation. However, data on the safety and efficacy of LFABs have accumulated steadily, and we now think that LFABs have clearly been demonstrated to be at least as efficacious as—and much safer than—AmBD. Indeed, we believe that only cost issues now prevent LFABs from becoming the standard of care. Clinicians and researchers should consider that these cost issues are clearly offset when considering the cost of renal failure, monitoring, and other complications, as well as the "enrollment cost" that has been associated with the use of AmBD. The many toxicities of AmBD might be tolerable in an otherwise healthy patient with a limited invasive mycosis, but the induction of even small amounts of nephrotoxicity in critically ill adults can be devastating. For example, a recent study examined outcomes of patients treated with AmBD and found that onset of acute renal failure during AmBD therapy increased the likelihood of death 6.6-fold [46]. Stated differently, an increase in the creatinine level from 1 to 3 mg/dL during treatment of cryptococcal meningitis in an otherwise healthy young adult is quite well tolerated, but a similar increase during therapy for invasive aspergillosis in patient with a hematological malignancy is associated with increased mortality [46, 47]. The use of LFABs as comparators during testing of new antifungal agents as initial therapy for invasive mycoses is the next logical step.

The recent licensing of new antifungal agents with high efficacy rates and minimal safety problems, such as caspofungin and voriconazole, will further complicate these issues. The use of AmBD and LFABs in the future may well be very limited as experience with these agents is accumulated.

ARE THERE SITUATIONS IN WHICH AMBD REMAINS USEFUL?

Despite the many advantages of LFABs, AmBD does retain some uses. First, it remains a standard option for intrathecal therapy of meningitis due to *Coccidioides immitis* [63]. Second, the lower AmB tissue levels produced in the kidney by LFABs (table 3) lead to a theoretical possibility of reduced efficacy at that site that should be kept in mind. Third, AmBD produces little nephrotoxicity in neonates, and its continued use for these patients seems appropriate [64, 65]. Fourth, brief low-dose courses of AmBD may be well tolerated by selected adults. For example, a recent analysis found a 28% rate of acute renal failure associated with AmBD therapy if the patient was either receiving cyclosporine, in an intensive care unit, or in an intermediate care unit at the time of initiation of therapy [66]. On the other hand, patients who lacked all of these risk factors had only an expected 4% rate of acute renal failure. Daily dose

was also relevant, and patients with any of those risk factors who also received ⩾30 mg of AmBD per day had a 33% rate of acute renal failure. Finally, rare individuals may actually tolerate AmBD better than LFABs [67].

CONCLUSIONS

Taken together, the aforementioned data on life-threatening fungal infections in a variety of patients, settings, and study designs can be summarized as follows: no study has ever shown an LFAB to be less effective than AmBD; some studies show strong evidence that LFABs may be more effective than AmBD; and LFABs are consistently less toxic than is AmBD.

These facts should make us reconsider our continued use of AmBD as both the therapeutic gold standard and as the standard comparator for clinical trials for antifungal agents. AmBD was, at the time of its introduction, a revolutionary drug. However, it is now clear that it can be reformulated in such a fashion that it retains potency while lessening its side effects. Nephrotoxicity is significant in that it may limit the use of truly therapeutic doses, and it is also associated with increased morbidity and mortality. Use of these safer versions of AmBD ultimately translates to improved efficacy, because a safer compound enables delivery of drug in maximum dosage, thus maximizing its potential benefit. And reductions in cumulative AmB-related nephrotoxicity preserve renal reserve, should the patient require other nephrotoxic therapies.

As far as clinical trials go, studies of new agents compared with an LFAB will actually be a better test of the true microbiological efficacy of the new agent, rather than becoming yet another demonstration of how the toxicity of AmBD limits its ability to treat infections. Doses of 3–6 mg/kg of LFABs would be appropriate (this includes the licensed dose range for the 3 currently marketed formulations). Doses at the lower end of the range appear to be appropriate for candidal infections [68, 69], and higher doses appear to be appropriate for treatment of mould infections and cryptococcal meningitis. Anecdotal and animal model evidence has shown that it is possible to use much higher doses safely; however, this is strongly discouraged until solid clinical trial data are released. Likewise, alternative dosing regimens, such as administration every other day and continuous infusions, should be further explored. Finally, the higher cost of LFABs appears generally to be offset by the reduced rates of nephrotoxicity.

As the medical community increasingly becomes aware of these advantages, use of LFABs appears destined to continue to accelerate. Even recent treatment guidelines mention their use as first-line therapy in certain defined situations [70, 71]. Formulary decisions regarding use of AmBD should begin to focus on encouraging use of LFABs for patients who cannot safely receive AmBD. If AmBD therapy is deemed to be safe in a particular patient, the physician should also remain alert to the possible need for a prompt switch to an LFAB if signs of nephrotoxicity develop. In addition, steps should be taken to ensure maximum renal protection. Aggressive hydration and electrolyte correction have been shown to greatly reduce the incidence of nephrotoxicity [72].

The best formulary choice of LFABs can be debated at length, but the issues can also be quickly summarized. ABCD's infusion-related toxicities have limited its acceptance. ABLC has a long history of use and is an excellent choice. LAmB is the other excellent and popular choice because of its wide array of indications; the data suggest reduced nephrotoxicity relative to ABLC and support the ability to escalate the dose in very serious infections [73]. More head-to-head clinical trails with standardized protocols of infusion and toxicity management are needed to clearly define which formulation is superior, if any.

The shared goal of industry, academicians, clinicians, and the US Food and Drug Administration is the development of safe and effective drug products as efficiently as possible. We believe that, to accomplish this goal and serve our patients' best interests, we should be using the safest and most effective drugs currently available as gold standards, both for clinical use and in clinical trials designed to explore and license the next generation of antifungal agents.

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