Clinical Medicine Reviews in Therapeutics

Libertas Academica
FREEDOM TO RESEARCH

CMR
Clinical Medicine Reviews

REVIEW

# Liposomal Amphotericin B: A Review of Its Use in the Treatment of Invasive Fungal Infections

T. Scott Warmack and Paul O. Gubbins

Department of Pharmacy Practice, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR.
Corresponding author email: twarmack@uams.edu

**Abstract:** Amphotericin B has been the mainstay of antifungal therapy for more than 50 years, but its associated toxicity often delayed or limited its use. In general, formulating this drug with phospholipids has greatly improved its safety and maintained its efficacy. In particular incorporating amphotericin B into a liposome produced a unique pharmacokinetic profile that altered its distribution, enhanced its safety and maintained its overall effectiveness in the treatment of infections due to pathogenic yeasts and invasive molds. Clinical trial experience and expert opinion suggest there are likely few differences between the lipid amphotericin B formulations. Although the composition of liposomal amphotericin B could improve the ability of amphotericin B to treat CNS fungal infections, to date human data do not completely corroborate findings in animals. This report summarizes the pharmacology, pharmacokinetics, clinical trial data and the Infectious Disease Society of America (IDSA) guidelines regarding the use of liposomal amphotericin B to treat systemic and invasive fungal infections.

**Keywords:** antifungal, liposomal amphotericin B, invasive fungal infections

*Clinical Medicine Reviews in Therapeutics* 2010:2 313–329

doi: 10.4137/CMRT.S5828

This article is available from http://www.la-press.com.

## Introduction

For more than 50 years, amphotericin B deoxycholate (AmBd) was the gold standard therapy for systemic fungal infections caused by a variety of opportunistic yeasts and invasive moulds. However, concerns regarding its narrow therapeutic index often tempered its use. The dose and infusion related toxicities of AmBd are renowned. The infusion-related toxicities (eg, hypotension, fever, rigors, and chills) occur frequently, often despite premedication with acetaminophen or nonsteroidal antiinflammatory agents, meperidine and hydrocortisone.[1] However, the frequency of these reactions lessen with repeated exposure.[1] More importantly infusion related toxicities rarely cause a cessation of therapy. However, dose-related adverse effects (eg, cardiac arrhythmias, anemia, renal failure, azotemia, renal tubular acidosis, and electrolyte imbalance) may be severe enough to limit therapy. Throughout its history there were many efforts to limit toxicity associated with AmBd, while maintaining the drug's efficacy. Many of these measures (ie, pre-medication, prolonging the infusion, every other day dosing, and pre- and post-infusion hydration) have variable effectiveness in minimizing AmBd toxicity, and they have their limitations.

A major advance in the effort to improve the therapeutic index of AmBd occurred in 1981 when it was demonstrated that incorporating amphotericin B into a variety of liposomal preparations comprised of various phospholipids improved the drug's therapeutic index without compromising its efficacy in a murine model of leishmaniasis.[2] Shortly thereafter, investigators reported that mice infected with *Cryptococcus neoformans* and treated with liposome-associated amphotericin B had reduced toxicity, prolonged survival and lower tissue counts of cryptococci than control animals.[3] These observations were the first to demonstrate the potential of liposomal amphotericin B to improve the drug's therapeutic index in the treatment of an opportunistic fungal infection. While several lipid formulations of amphotericin B exist, the purpose of this manuscript is to review the pharmacology, safety and efficacy of liposomal amphotericin B (L-AmB).

## Liposomal Amphotericin B Pharmacolgy

### Liposomes—basic structure and function

The discovery of liposomes is attributed Bangham et al, who in 1965 described the microscopic bilayer vesicles that formed when phospholipids were placed in an aqueous environment.[4] Since then, the application of liposomes in medical practice have been diverse and versatile in nature. L-AmB is an example of the application of a conventional liposome to increase the therapeutic index of a toxic but effective antifungal agent. Conventional liposomes are composed only of phospholipids and/or cholesterol. The particular phospholipid and cholesterol components are critical to the structure and function of the bilayer as a drug delivery mode. How a liposome behaves in the body depends upon its size, bilayer rigidity or stability, surface charge, and morphology.

Phospholipids are amphiphilic molecules that contain a three-carbon glycerol backbone. To ultimately form the bilayer, a polar hydrophilic head group is attached to the first glycerol carbon and two hydrophobic fatty acid side chains are linked to the other two glycerol carbons. Thus, when placed in an aqueous environment the polar head interacts with water and orients to form the outer surfaces of the bilayer. The fatty acid side chains orient to form the inner bilayer and interact with the side chains of the other phospholipid molecules, and perhaps the drug itself, to stabilize the liposome. The stability of a liposome depends on its constituent phospholipids. With increasing temperature, pure phospholipids undergo phase transition from an ordered, rigid gel state to a less ordered, more permeable liquid crystalline state.[5] The phase transition temperature depends upon the fatty acid chain length, the degree of unsaturation in each carbon side chain, and the nature of the head group.[6] Bilayers containing more saturated phospholipids have higher phase transition temperatures and are more rigid and less permeable than those containing less saturated or unsaturated phospholipids. Liposomal bilayers release their contents at or above their transition temperatures. Thus, if the liposome is designed to transport drugs throughout the body, they must be prepared from phospholipids with phase transition temperatures in excess of 37C.

Cholesterol is generally added to the phospholipids in a high molar fraction to significantly increase the stability of the liposome and thereby reduce the potential to leak their contents.[5] Cholesterol inhibits the crystallization of the hydrocarbon chains of saturated lipids, which prevents transition to a permeable liquid crystalline state and results in the formation

of a rigid gel state system.[7,8] The surface charge of the liposome is also a determinant of liposomal stability. Charged phospholipids are frequently used in formulations to prevent the aggregation of uncharged liposomes in an aqueous suspension. However, due to electrostatic interactions with oppositely charged surfaces, charged liposomes may be more permeable to solutes than uncharged liposomes.[5]

## Liposomal amphotericin B composition

Unlike other marketed lipid formulations of amphotericin B, which are colloid drug-lipid complexes, L-AmB is a small (<100 nm in diameter) unilamellar vesicle. L-AmB is composed of hydrogenated soy phosphatidylcholine (HSPC), cholesterol and distearoyl phosphatidylglycerol (DSPG) combined with amphotericin B in a 2:1:0.8:0.4 molar ratio.[9] HSPC and DSPG are saturated, and therefore have phase transition temperatures above 50C, which provides stabilization and prevents leakage.[6] In addition to stabilizing the membrane, cholesterol interacts with amphotericin B and may provide added stability by holding the drug within the liposome.[6,10] While HSPC has no net charge, DSPG is negatively charged and may also provide additional stability through its ionic interactions with the amine group of amphotericin B.[6]

## Pharmacokinetics of liposomal amphotericin B

In humans, the mononuclear phagocyte system (MPS) functions to efficiently clear foreign particles including liposomes from circulation. Like liposomes, amphotericin B is cleared by the cells of the MPS.[11] This system is comprised primarily of tissue-based macrophages that are broadly distributed in the body (ie, Kupffer cells of the hepatic sinusoids, reticular cells of the lymphatic tissue, bone marrow, lung, etc), but are most prevalent in the liver and spleen.[7] Following intravenous administration, liposomes interact with, or are coated with plasma proteins, which can destabilize the lipid bilayer or coat its surface and enhance phagocytosis.[7] Physicochemical properties (size, surface charge, composition and stability) of the liposome also determine how long they circulate in the blood. In general, small liposomes (<200 nm diameter) circulate longer than large liposomes.[5,7] Particle size is an important determinant of liposomal pharmacokinetic behavior largely for mechanical reasons. Larger molecules may lodge in the capillaries.[5,12–15] In addition the liver and spleen are major organs of the MPS and they both have a rich blood supply to deliver the particles (ie, liposomes) and an abundance of tissue macrophages to remove many particles. A small particle size aids in the ability to avoid the macrophage rich tissues of the liver (Kupffer cells) and spleen. Small unilamellar vesicles (SUVs) like L-AmB, are able to extravasate through the fenestrations in the endotheilium in the liver sinusoids and to interact with the liver parenchymal cells.[5,12–15] In some cases SUVs can be internalized by hepatic parenchymal cells via pinocytosis and therefore avoid significant uptake and removal by phagocytic cells. Although critically important, size alone does not determine the circulation time of a liposome. Charged liposomes, particularly negatively charged surfaces, promote protein binding, which enhances phagocytosis and rapid removal from the circulation.[5,12–15]

Amphotericin B is highly protein bound (>95%) primarily to albumin and α1-acid glycoprotein. Following L-AmB administration most of the amphotericin B in plasma remains associated with the liposome and very little exists as unbound drug.[16] Due to its small size and composition, compared to other lipid amphotericin B formulations L-AmB is cleared more slowly from the bloodstream; has a longer circulation half-life; and achieves higher maximum plasma concentration and systemic drug exposure.[17,18] Very little of an administered dose is recovered unchanged in the urine or feces.[18] Although incorporating amphotericin B into the liposome markedly reduces the total urinary and fecal recoveries of the drug, it does not affect unbound amphotericin B urinary and fecal drug clearances. Thus, sequestering amphotericin B into a long-circulating liposome increases total amphotericin B plasma concentrations while decreasing its unbound plasma concentrations.[18]

Similar to the colloidal AmBd, L-AmB exhibits a triphasic plasma concentration profile, and the half-lives of each phase are similar between each formulation. However, the terminal elimination phase of L-AmB accounts for only 47% of its total exposure whereas it accounts for 80% of AmBd total exposure.[17] This suggests that the earlier phases of L-AmB disposition (sequestration in the plasma compartment, and distribution to the tissue compartment) account

for a majority of its overall pharmacokinetic profile.[18] Furthermore, less than 10% of a L-AmB dose is recovered in the urine and feces, whereas nearly 67% recovery of an AmBd dose from the urine and feces.[18] These data reflect the formulations are handled differently by the MPS and illustrate how incorporating amphotericin B into a liposome alters its distribution and subsequent excretion.

L-AmB has a smaller volume of distribution than the other lipid amphotericin B formulations. However, there are limitations to using calculated volume of distribution to interpret the pharmacokinetic behavior of liposomal drugs like L-AmB. Pharmacokinetically calculated volume of distribution significantly underestimates physiologic volume of distribution of liposomal drugs.[19] Liposomal uptake into tissues can occur via several mechanisms, and may not involve an equilibrium distributional process whereby the liposome can freely diffuse rapidly back into the circulation.[19] Therefore, since plasma and tissue liposome concentrations likely do not decline in parallel during the post-distributional elimination phase, pharmacokinetically calculated volume of distribution reflects circulating liposomes rather than the extent of tissue distribution.[19]

Each lipid formulation of amphotericin B has a distinct composition that produces different plasma pharmacokinetics in the body. There are few data describing amphotericin B disposition in human tissue following administration of L-AmB. Thus, whether the unique plasma pharmacokinetics of L-AmB in humans translates into different disposition patterns in distinct tissues or enhanced clinical efficacy relative to the other formulations is largely unknown. Data from autopsy material of patients who had been treated for suspected or proven invasive fungal infection with L-AmB or the colloidal-drug complex, amphotericin B colloidal dispersion (ABCD) suggest individual differences in the formulations may influence drug penetration into the lung and perhaps the kidney.[20] Amphotericin B lung concentrations in patients treated with ABCD significantly exceeded those treated with L-AmB.[20] High concentrations of both formulations were found in the liver and spleen, whereas lower concentrations were observed in the myocardium and kidney.[20] However, even though amphotericin B kidney concentrations were lower than other sites, renal concentrations produced by ABCD significantly exceeded those of produced by L-AmB.[20]

L-AmB tissue concentrations have been compared to those following administration of other amphotericin B formulations in a variety of animals, particularly rabbits. Like plasma, in the lungs of rabbits the lipid formulations of amphotericin B demonstrated distinct pulmonary disposition patterns.[21] Compared to AmBd, L-AmB produced higher concentrations in epithelial lining fluid (ELF), and pulmonary tissue, and comparable concentrations in pulmonary alveolar macrophages (PAM) and peripheral blood monocytes (PBM).[21] Among all lipid formulations, L-AmB produced the highest amphotericin B concentrations in ELF, whereas its concentrations in pulmonary tissue, PAMs were comparable to ABCD, and much lower than amphotericin B lipid complex (ABLC).[21] ABCD produced the highest concentrations among all amphotericin B formulations in PBMs.[21] The animals in this study were uninfected so a therapeutic advantage cannot be discerned.

The central nervous system (CNS) disposition and antifungal efficacy of all the lipid-amphotericin B formulations have also been studied in a rabbit model. Amphotericin B penetration into the CNS following administration of a lipid-amphotericin B formulation is likely a function of a concentration gradient between the plasma and CNS.[22] Therefore formulations that do not achieve high and sustained unbound amphotericin B concentrations in the plasma may not be successful in eradicating susceptible fungi from the CNS.[22] Even though in the plasma very little L-AmB circulates as unbound drug,[16] of the three lipid-amphotericin B formulations, L-AmB achieves the highest and most sustained concentrations of free compound in the plasma; consequently, it was the most successful in eradicating *C. albicans* from brain tissue.[22] These data are consistent with findings in human cryptococcal meningitis.[23] The extent to which L-AmB distributes into bone marrow and liver of uninfected rabbits is comparable to the other lipid-amphotericin B formulations, but it is much greater than AmBd.[24] However, all lipid-amphotericin B formulations accumulate poorly within fat tissue uninfected rabbits.[24]

The limitations of tissue and ELF concentration data in humans and animals are well described, and these data should be interpreted cautiously.[25–27] The transfer of drug from plasma to tissues and biological

fluids is heterogeneous and tissue/fluid specific throughout the body.[25,27] Therefore, clinicians should understand studies measuring L-AmB concentrations in human tissue and biological fluids have limitations and their results often cannot be extrapolated to other tissues and biological fluids at other anatomical sites. For example, whole biopsy tissue concentrations are often obtained by homogenizing the biopsy sample and determining the concentration of drug in the tissue homogenate. Tissues are comprised of several distinct compartments, and the homogenization process destroys these distinct compartments, yielding a uniform concentration in solution. However, in intact tissue the drug may not be homogeneously distributed among the distinct compartments.[25] Therefore, the concentrations represent the overall concentration in the tissue homogenate and do not necessarily represent the active concentration at the infection site.[25] Moreover, with the destruction of distinct tissue compartments, there can be contamination from associated tissue or biological fluid compartments.[25–27] Nonetheless, studies of drug concentration in tissue and biological fluids do provide basic data to characterize how the body handles a particular drug, and helps scientists design additional studies employing specific techniques (ie, microdialysis) to further characterize drug disposition. A comprehensive review of the benefits and limitations of tissue and biological fluid concentration data is beyond the scope of this review. This topic has been well reviewed elsewhere.[25–27]

## Clinical Efficacy

L-AmB has been studied in prospective, randomized trials as treatment for invasive fungal infections and empiric therapy in febrile neutropenia. (Tables 1–4) Additionally, clinical practice guidelines have been published by the Infectious Disease Society of America (IDSA) for the management of aspergillosis, candidiasis, cryptococcal disease, histoplasmosis.

### Aspergillosis

Studies assessing the efficacy and safety of L-AmB for the treatment of pulmonary and invasive aspergillosis are summarized in Table 1. The efficacy of L-AmB has been described in two small studies of neutropenic hosts with either suspected or documented pulmonary aspergillosis or invasive aspergillosis. One study compared the efficacy of L-AmB (5 mg/kg/day) to that of AmBd (1 mg/kg/day) each given for two weeks followed by 3/mg/kg/day to complete therapy of suspected or documented pulmonary aspergillosis.[28] Response rates following 14 days of therapy were higher for patients treated with L-AmB (52% vs. 29%, $P = 0.096$), however the difference was not statistically significant. The difference in response rate at completion of therapy was similar (42% and 21%) with L-AmB and AmBd, respectively ($P = 0.14$).

In the other study, neutropenic patients with probable invasive aspergillosis received either L-AmB 1 or 4 mg/kg/day for 14 days.[29] No significant differences in clinical response (partial or complete) were observed by end of therapy (64% vs. 48%, $P = 0.144$). Similarly there was no difference in radiological response (58% vs. 54%, $P = 0.694$) nor survival between the groups. In this study the response rate for L-AmB in the treatment of suspected or proven invasive aspergillosis was similar to that reported for other antifungal agents (approximately 40%–50%).[30] The investigators concluded that because L-AmB 1 mg/kg/day was as effective as 4 mg/kg/day and there was no advantages to the use of the higher, more expensive, dosages. However, the study contained suspected cases and when only the patients with proven invasisve aspergillosis are considered the trend toward improved response in patients who were treated with the higher dosage is no longer evident. In the study there were only 10 evaluable proven cases, (n = 4 in the 1 mg/kg/day). In both groups there were 3 treatment failures.[29] Thus, in this study there were too few cases to draw any firm conclusions regarding a dose-response relationship.[30]

A larger (n = 201) randomized trial of patients with proven or probable invasive mold infection compared standard dose L-AmB (3 mg/kg/day) to high dose L-AmB(10 mg/kg/day) for 14 days, followed by 3 mg/kg/day.[31] Ninety three percent of patients had hematological malignancies, and 97% had proven or probable invasive aspergillosis. There was no significant difference reported between the two dosage groups for the primary endpoint of favorable overall response (50% standard dose vs. 46% high dose, $P = 0.65$) or survival at 12 weeks (72% standard dose vs. 59% high dose) or at the end of therapy (93% standard dose vs. 88% high dose).

Historically the success of antifungal therapy of invasive aspergillosis has been dismal. The outcome

**Table 1.** Summary of clinical trials of L-AmB for invasive and pulmonary aspergillosis.

| Reference | Trial design | Patients | L-AmB dose | Comparator | Efficacy outcomes | Safety outcomes |
|---|---|---|---|---|---|---|
| Leenders AC et al.[28] | R, MC | n = 53<br>Neutropenic with documented or suspected invasive fungal infections (analysis of patients with suspected/documented pulmonary apergillosis) | 5 mg/kg/d × 14 days, then 3 mg/kg/d | AmBd 1 mg/kg/d, then 0.7 mg/kg/d | Overall response—14 d<br>• L-AmB5 52% vs. AmBd 29%, $P = 0.096$<br>Overall response—Completion of therapy<br>• L-AmB5 42% vs. AmBd 21%, $P = 0.14$<br>Mortality<br>• L-AmB5 20% vs. AmBd 40%, $P = 0.15$ | Doubling of SCr<br>• L-AmB 11.5% vs. AmBd 40.7%, $P < 0.001$ |
| Ellis M et al.[29] | R, MC | n = 87<br>Neutropenic with probable IA (30% with proven IA) | 4 mg/kg/d for at least 14 d | L-AmB 1 mg/kg/d for at least 14 d | Overall response<br>• L-AmB1 64% vs. L-AmB4 48%, $P = 0.144$<br>Radiologic response<br>• L-AmB1 58% vs. L-AmB4 54%, $P = 0.694$<br>2 wk survival<br>• L-AmB1 69% vs. L-AmB 81%, $P =$ NS<br>2 mo survival<br>• L-AmB1 58% vs. L-AmB 51%, $P =$ NS<br>6 mo survival<br>• L-AmB1 43% vs. L-AmB 37%, $P =$ NS | No significant differences in adverse effects reported |
| Cornely OA et al.[31] | R,DB, MC | n = 201<br>Proven or probable invasive mold infection (confirmed aspergillus in 97%; hematologic malignancies in 93%) | 3 mg/kg/d until the EOT. | L-AmB 10 mg/kg/d × 14 d, then 3 mg/kg/d until the EOT. | Response rates<br>• Overall: L-AmB3 50% vs. L-AmB10 46%, CI 95% −10 to 18; $P = 0.65$<br>• Probable aspergillus: L-AmB3 56% vs. L-AmB10 48%, (CI 95% −10 to 26)<br>• Confirmed aspergillus: L-AmB3 50% vs. L-AmB10 46%, (CI 95%, −10 to 18)<br>12 wk survival<br>• L-AmB3 72% and L-AmB10 59%, CI 95%–0.2% to 26%; $P > 0.05$ | Discontinuation due to toxicity<br>• L-AmB3 20% vs. L-AmB10 32%, $P = 0.035$<br>Increase in SCr<br>• L-AmB3 10% vs. L-AmB10 27%, CI 95% −27 to −7, $P = 0.002$<br>Doubling of SCr<br>• L-AmB3 14% vs. L-AmB10 31%, CI 95% −28 to −5, $P = 0.005$<br>No significant difference in infusion related reactions |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Combination therapy** | | | | | | |
| Caillot D et al.[33] | R, OL, MC | n = 30<br>Hematologic malignancies and with proven or probable IA<br>13% with proven IA | 10 mg/kg/d | L-AmB 3 mg/kg/d + Caspo 70 mg [1d], then 50 mg/d | Overall response rate<br>• L-AmB10 27% vs. combo 67%, $P = 0.028$<br>12 wk survival<br>• L-AmB10 80% vs. combo 100%, $P$ = NS | No significant differences in adverse effects reported |

**Table 2.** Summary of clinical trials of L-AmB for candidemia and invasive candidiasis.

| Reference | Trial design | Patients | L-AmB dose | Comparator | Efficacy outcomes | Safety outcomes |
|---|---|---|---|---|---|---|
| Kuse ER et al.[34] | R, MC, DB | n = 392<br>Candidemia or invasive candidiasis | 3 mg/kg/d | Mica 100 mg/d | EOT success (clinical and mycologic)<br>• L-AmB3 89.5% vs. mica 89.6%, CI 95%, –5.3 to 6.7<br>Mycologic persistance at EOT<br>• L-AmB3 9% vs. mica 9% | Discontinuation due to toxicity<br>• L-AmB3 9.0% vs. Mica 4.2%, $P = 0.087$<br>Increased SCr<br>• L-AmB3 6.4% vs. Mica 1.9%, $P = 0.015$<br>SCr > ULN<br>• L-AmB3 29.9% vs. Mica 10.3%, $P = 0.0001$<br>SCr > 2 × ULN<br>• L-AmB3 3.7% vs. Mica 2.1%, NS, $P = 0.509$<br>Infusion-related reaction<br>• L-AmB3 28.8% vs. Mica 17.0%, $P = 0.001$<br>Fever<br>• L-AmB3 6.4% vs. Mica 0.8%, $P = 0.0006$ |
| Queiroz-Telles F et al.[35] | R, MC, DB | n = 98<br>Candidemia or invasive candidiasis | 3 mg/kg/d | Mica 2 mg/kg/d | Treatment success (clinical and mycologic) at EOT<br>• L-AmB3 6% vs. mica 72.9%, CI 95%, –20.0 to 15.3 | Discontinuation due to toxicity<br>• L-AmB3 16.7% vs. Mica 3.8%, $P = 0.05$ |

**Table 3.** Summary of clinical trials of L-AmB for cryptococcal meningitis and histoplasmosis.

| Reference | Trial design | Patients | L-AmB dose | Comparator | Efficacy outcomes | Safety outcomes |
|---|---|---|---|---|---|---|
| **Cryptococcal meningitis** | | | | | | |
| Leenders AC et al.[23] | R | n = 28 HIV-infected patients with cryptococcal meningitis | 4 mg/kg/d × 3 wks, then FCZ for 7 wks | AmBd 0.7 mg/kg/d × 3 wks, then FCZ for 7 wks | Clinical success—3 wks<br>• L-AmB4 80% vs. AmBd 86%, $P = NS$<br>Clinical success—10 wks<br>• L-AmB4 87% vs. AmBd 83%, $P = NS$<br>CSF conversion—1 wk<br>• L-AmB4 40% vs. AmBd 8%, $P = 0.09$<br>CSF conversion—2 wks<br>• L-AmB4 67% vs. AmBd 11%, $P = 0.01$ | Less rise in SCr from baseline with L-AmB<br>• Average rise in SCr 1.37 X more with AmBd |
| Hamil RJ et al.[37] | R, DB, MC | n = 267 HIV-infected patients with cryptococcal meningitis | 3 mg/kg/d or 6 mg/kg/d × 14 d, then FCZ 400 mg to complete 10 wks | AmBd 0.7 mg/kg/d × 14 d, then FCZ 400 mg to complete 10 wks | Clinical success—2 wks<br>• L-AmB3 65.8% vs. L-AmB6 75.3% vs. AmBd 65.8%, $P = NS$<br>Clinical success—10 wks<br>• L-AmB3 70.5% vs. L-AmB6 72.9% vs. AmBd 81.5%, $P = NS$<br>CSF conversion—2wks<br>• L-AmB3 58% vs. L-AmB6 48% vs. AmBd 47.5%, LAmB3 vs. AmBd CI 95%, −6.9 to 28.5; LAmB6 vs. AmBd CI 95%, −16.4 to 17.3<br>Therapeutic success—10 wks<br>• L-AmB3 67.5% vs. L-AmB6 73.7% vs. AmBd 75.5%; LAmB3 vs. AmBd CI 95%, −26.6 to 10.6; LAmB6 vs. AmBd CI 95%, −18.1 to 14.5<br>Survival—10 wks<br>• L-AmB3 86% vs. L-AmB6 90.4% vs. AmBd 88.5%, $P = NS$ | Discontinuation due to toxicity<br>• L-AmB3 3.5% vs. L-AmB6 2.1% vs. AmBd 4.6%, $P = NS$<br>Doubling of SCr<br>• L-AmB3 14.9% vs. L-AmB6 21.3% vs. AmBd 33.3%; $P = 0.004$ L-AMB3 vs. AmBd, $P = NS$ L-AmB6 vs. AmBd<br>Infusion–related reactions-overall<br>• L-AmB3 31.4% vs. L-AmB6 37.2% vs. AmBd vs. 66.7%; both comparisons $P < 0.001$<br>Increase temp > 1.0 C<br>• L-AmB3 7% vs. L-AmB6 8.5% vs. AmBd 27.6%; both comparisons $P < 0.001$<br>Chills/and or rigors<br>• L-AmB3 5.8% vs. L-AmB6 8.5% vs. AmBd 48.3%; both comparisons $P < 0.001$<br>K < 3.0<br>• L-AmB3 9.3% vs. L-AmB6 35.1% vs. AmBd 29.9%; $P = 0.001$ L-AMB3 vs. AmBd, $P = NS$ L-AmB6 vs. AmBd |
| **Histoplasmosis** | | | | | | |
| Johnson PC et al.[39] | R, DB, MC | n = 73 Patients with AIDS and moderately severe disseminated histoplasmosis | 3 mg/kg/d induction therapy × 14 d, followed by 10 wks of ITZ | AmBd 0.7 mg/kg/day induction therapy × 14 d, followed by ITZ × 10 wks | Clinical success rates at 2 wks<br>• L-AmB3 88% vs. AmBd 64%, CI 95%, 1 to 52; $P = 0.014$<br>Survival during induction (14 d)<br>• L-AmB3 98% vs. AmBd 87.5%, CI 95% 6 to 37, $P = 0.04$ | Doubling of SCr<br>• L-AmB3 9% vs. AmBd 37%, $P = 0.003$<br>Infusion-related reactions-overall<br>• L-AmB3 25% vs. AmBd 63%, $P = 0.002$ |

**Table 4.** Summary of clinical trials of L-AmB for febrile neutropenia.

| Reference | Trial design | Patients | L-AmB dose | Comparator | Efficacy outcomes | Safety outcomes |
|---|---|---|---|---|---|---|
| Walsh TJ et al.[41] | R, DB | n = 687 Persistent fever and neutropenia | 3 mg/kg/d | AmBd 0.6 mg/kg/d | Overall response rate<br>• L-AmB3 50.1% vs. AmBd 49.4%, $P$ = NS<br>Absence of breakthrough fungal infections<br>• L-AmB3 81.8% vs. AmBd 72.7%, $P$ = NS<br>Proven breakthrough fungal infections<br>• L-AmB3 3.2% vs. AmBd 7.8%, $P$ = 0.009<br>Fever resolution<br>• L-AmB 58% vs. AmBd 58.1%, $P$ = NS<br>1 wk survival<br>• L-AmB3 92.7% vs. AmBd 89.5%, $P$ = NS | Toxicity-related discontinuation of therapy<br>• L-AmB3 14.3% vs. AmBd 18.9% (NS)<br>Doubling of SCr<br>• L-AmB3 18.7% vs. AmBd 33.7%, $P < 0.001$<br>SCr $> 1.5 \times$ baseline<br>• L-AmB3 29.4% vs. AmBd 49.4%, $P < 0.001$<br>SCr $> 3.0 \times$ baseline<br>• L-AmB3 8.2% vs. AmBd 16.6%, $P < 0.001$<br>Fever on day 1<br>• L-AmB3 17% vs. AmBd 44%, $P < 0.001$<br>Chills or rigors on day 1<br>• L-AmB3 18% vs. AmBd 54%, $P < 0.001$<br>Flushing<br>• L-AmB3 5.2% vs. AmBd 0.6%, $P < 0.01$<br>K $< 2.5$ mEq/L<br>• L-AmB3 6.7% vs. AmBd 11.6%, $P < 0.05$ |
| Wingard et al.[42] | R, DB | n = 244 Persistent fever and neutropenia | 3 mg/kg/d or 5 mg/kg/d | ABLC 5 mg/kg/d | Overall response rate<br>• L-AmB3 40% vs. L-AmB5 42% vs. ABLC 33%, $P$ = NS | Toxicity-related discontinuation of therapy<br>• L-AmB3 12.9% vs. L-AmB5 12.3% vs. ABLC 32.1%; $P \leq 0.01$ for both comparisons<br>Doubling of SCr<br>• L-AmB3 14.1% vs. L-AmB5 14.8% vs. ABLC 42.3%; $P < 0$ .01 for both comparisons<br>Fever on day 1<br>• L-AmB3 23.5% and L-AmB5 19.8% vs. ABLC 57.7% ; $P < 0.001$ for both comparisons<br>Chills/rigors on day 1<br>• L-AmB3 18.8% and L-AmB5 23.5% vs. ABLC 79.5%; $P < 0.001$ for both comparisons<br>Chills/rigors after day 1<br>• L-AmB3 21.0% and L-AmB5 24.3% vs. ABLC 50.7%; $P < 0.001$ for both comparisons |

(*Continued*)

**Table 4.** (*Continued*).

| Reference | Trial design | Patients | L-AmB dose | Comparator | Efficacy outcomes | Safety outcomes |
|---|---|---|---|---|---|---|
| Walsh TJ et al.[43] | R, DB | n = 1095 Persistent fever and neutropenia | 3 mg/kg/d | Caspo 70 mg [1d], then 50 mg/d | Overall response rate<br>• L-AmB 33.7% vs. Caspo 33.9% (95% CI, −5.6 to 6.0)<br>Response with baseline fungal infection<br>• L-AmB3 25.9% vs. 51.9%, $P = 0.04$<br>1 wk survival<br>• L-AmB3 89.2% vs. Caspo 92.6%, $P = 0.05$ | Toxicity-related discontinuation of therapy<br>• L-AmB3 8.0% vs. Caspo 5.0%; $P = 0.04$<br>Doubling of SCr<br>• L-AmB3 11.5% vs. Caspo 2.6%, $P < 0.001$<br>Infusion-related events<br>• L-AmB3 51.6% vs. Caspo 35.1%, $P < 0.001$ |
| Walsh et al.[44] | R, NB | n = 837 Persistent fever and neutropenia | 3 mg/kg/d | VCZ 6 mg/kg load, then 3 mg/kg q 12h | Overall response rate<br>• L-AmB3 31% vs. Vori 26% (95% CI, −10.6 to 1.6%)<br>Breakthrough fungal infections<br>• L-AmB3 1.9% vs. Vori 5%, $P = 0.02$<br>1 wk survival<br>• L-AmB3 92% vs. Vori 94.1%; 95% CI −5.5 to 1.4% | Toxicity-related discontinuation of therapy<br>• L-AmB3 9.9% vs. VCZ 6.6%, $P =$ NS<br>Doubling of SCr<br>• L-AmB3 7.6% vs. VCZ 7.0%, $P =$ NS<br>Scr $> 1.5 \times$ baseline<br>• L-AmB3 19.0% vs. VCZ 10.4%, $P < 0.001$<br>Chills<br>• VCZ 13.7% vs. L-AmB3 29.9%, $P < 0.001$<br>Chest pain<br>• VCZ 0.2% vs. L-AmB3 4.0%, $P < 0.001$<br>Abdominal pain<br>• VCZ 0.2% vs. L-AmB3 2.8%, $P = 0.002$<br>Back pain<br>• VCZ 0% vs. L-AmB3 3.3%, $P < 0.001$<br>Flank pain<br>• VCZ 0.2% vs. L-AmB3 1.9%, $P = 0.038$<br>Dyspnea<br>• VCZ 0.7% vs. L-AmB3 8.8%, $P = 0.001$<br>Anaphylactoid reaction<br>• VCZ 0% vs. L-AmB3 1.7%, $P = 0.02$<br>Flushing<br>• VCZ 3.4% vs. L-AmB3 10.9%, $P < 0.001$ |

**Abbreviations:** DB, double blind; MC, multicenter; OL, open label; R, randomized; IA, invasive aspergillosis; d, day(s); EOT, end of therapy; wk(s), week(s); mo, month(s); FCZ, fluconazole; ITZ, itraconazole; VCZ, voriconazole; AmBd, amphotericin B deoxycholate; L-AmB, liposomal amphotericin B; ABLC, amphotericin B lipid complex; Caspo, caspofungin; Mica, micafungin; NS, not statistically significant; SCr, serum creatinine.

of antifungal therapy in invasive aspergillosis depends upon how well the host's immune status and underlying disease are concurrently controlled. This may explain in part why advances in antifungal therapy have not necessarily improved the outcome of invasive aspergillosis.[32] An advantage to the any lipid amphotericin B formulation over AmBd is that large doses can be employed for prolonged times with lower rates of side effects. However, in the treatment of invasive aspergillosis the most effective dose and duration of any lipid amphotericin B formulation has not been firmly established by comparative studies properly powered to determine efficacy.[30] The studies to date involving L-AmB suggest there are no advantages to the use of higher than recommended doses. Nonetheless, due to the improved overall safety of L-AmB relative to AmB-d, many clinicians may use higher than recommended L-AmB dosage ranges despite a lack of evidence establishing a dose response relationship. In fact, in the largest study of L-AmB dosing greater toxicity was observed in the higher-dosage group.[30,31] The dose-response relationship of L-AmB in the treatment of invasive aspergillosis is poorly studied and will likely not be known until rigorous studies in which the host's immune status and underlying disease are concurrently controlled.

L-AmB as combination therapy with other antifungal agents has been evaluated in a small pilot study.[33] Thirty immunocompromised patients with invasive aspergillosis were randomized to receive 10 mg/kg/day L-AmB or a combination of 3 mg/kg/day with caspofungin 70 mg on day one, then 50 mg daily. Therapy was continued for at least 14 days. At the end of therapy, the overall response was higher with combination therapy than with the monotherapy (67% vs. 27%, $P = 0.028$). No difference in survival was noted at week 12 or at the end of therapy.

The 2008 IDSA clinical practice guidelines for the treatment of aspergillosis recommend L-AmB (3–5 mg/kg/day) induction therapy as an alternative for patients with invasive aspergillosis who cannot tolerate voriconazole (recommendation graded as "AI").[30] L-Amb is also recommended as primary therapy for preemptive and empirical antifungal therapy and as an option for option for salvage therapy for invasive aspergillosis (recommendation graded as "AII").

## Candidiasis

Studies assessing the efficacy and safety of L-AmB for the treatment of candidemia and invasive candidiasis are summarized in Table 2. L-AmB has been compared to micafungin in the treatment of invasive candidiasis and candidemia in adults and pediatric patients. A randomized study in adults (n = 392) compared L-AmB 3 mg/kg/day or micafungin 100 mg daily for at least 14 days.[34] At the end of therapy, micafungin demonstrated non-inferiority to L-AmB for the primary endpoint of overall treatment success. The between group difference in the per-protocol population was 0.1% (95% CI, −5.9 to 6.2). After stratification by baseline neutropenic status, the between group difference was 0.7% (95% CI, −5.3 to 6.7). Moreover, an intention to treat and modified intention to treat analysis also demonstrated non-inferiority of micafungin. Mycologic persistence at the end of therapy was identical between both groups (9% vs. 9%) and there was no significant difference in mortality reported between the groups in the intention to treat analysis (18% micafungin vs. 17% L-AmB).

In a similarly designed sub study, pediatric patients with systemic *Candida* infection were randomized to receive L-AmB 3 mg/kg/day or micafungin 2 mg/kg/day for at least fourteen days.[35] While not powered to assess non-inferiority of micafungin, similar response rates were observed between the groups (76% L-AmB vs. 72.9%).

According to the 2009 IDSA clinical practice guidelines for Candidiasis L-AmB is included in the recommendations as a primary agent in neutropenic hosts, and as an alternative agent in confirmed candidiasis (recommendation graded as "AI") and suspected candidiasis (recommendation graded as "BIII") in nonneutropenic hosts, endophthalmitis (recommendation graded as "BIII") and neonatal candidiasis (recommendation graded as "BIII"). In the neutropenic host the guidelines recommend a lipid formulation amphotericin B (3–5 mg/kg/day) as one of two acceptable choices for primary therapy for candidemia (recommendation graded as "AII") or one of two acceptable choices with recommendation graded as "AI"for suspected candidiasis.[36] Lipid formulations are also recommended as primary therapy for chronic disseminated candidiasis (recommendation graded as "AIII"), in acutely ill patients or

patients with refractory disease.[36] Lipid formulations including L-AmB are also recommended as primary therapy in a variety of other forms of candidiasis including, osteoarticular, CNS, and cardiovascular infections, the evidence supporting their use in these infections is less robust (recommendation graded as "BIII").

## Cryptococcal meningitis

Studies assessing the efficacy and safety of L-AmB for the treatment of cryptococcal meningitis and Histoplasmosis are summarized in Table 3. Two trials have compared L-AmB to AmBd for the treatment of HIV-associated cryptococcal meningitis. In a small study, 28 patients were randomized to receive L-AmB 4 mg/kg/day or AmBd 0.7 mg/kg/day for three weeks, followed by 400 mg oral fluconazole for 7 weeks.[23] Culture conversion rates were higher with L-AmB within 7 (40% vs. 8%, $P = 0.09$), and 14 days (67% vs. 11%, $P = 0.01$). However, clinical response rates at 3 (80% L-AmB vs. 86% AmBd) and 10 weeks (87% L-AmB vs. 83% AmBd) were similar in both groups. A larger (n = 267) randomized study compared L-AmB 3 mg/kg/day or 6 mg/kg/day to AmBd 0.7 mg/kg/day as induction therapy, followed by oral fluconazole 400 mg to complete 10 weeks.[37] Regardless of dosage, L-AmB demonstrated non-inferiority to AmBd for mycological success at 2 weeks. Therapeutic success at 10 weeks, defined as clinical success plus CSF culture sterilization, did not meet the criteria for non-inferiority (67.5% vs. 75.5%; 95% CI for between-group difference = –26.5 to 10.6). No significant difference in 10 week mortality between groups was reported. However, the limitations to this study must be considered. The study was carried out approximately a decade before it was published. At the time the study was conducted highly active antiretroviral (HAART) therapy was in its infancy and its benefits and impact on the incidence of opportunistic infections such as cryptococcal meningitis. In fact, the study did not meet its targeted sample accrual goals because HAART therapy became widespread during this study.[37]

The 2010 IDSA clinical practice guidelines for cryptococcal disease recommends either L-AmB or ABLC as primary induction therapy for CNS infections in HIV–infected individuals with or at risk for renal dysfunction (recommendation graded as "BII") and organ transplant recipients (recommendation graded as "BII"),[38] severe pulmonary cryptococcosis (recommendation graded as "BIII") and cryptococcemia (recommendation graded as "BIII"). The recommended dose for L-AmB is 3–4 mg/kg/day plus flucytosine 100 mg/kg/day. Treatment duration should be at least 2 weeks if given with flucytosine, or 4–6 weeks if used as monotherapy. Because of the risk of nephrotoxicity solid organ transplant recipients, the guidelines stressed the use of a lipid amphotericin B in this population. The guidelines specifically cautioned against the use of AmBd and explicitly excluded it as a recommended as first-line agent in this patient population.[38]

## Histoplasmosis

L-AmB was compared to AmBd in a randomized study of 73 patients with moderate to severe AIDS-associated histoplasmosis.[39] Patients received induction therapy with either L-AmB 3 mg/kg/day or AmBd 0.7 mg/kg/day for 14 days, followed by 10 weeks of itraconazole. At the end of induction therapy, there was a higher response rate with L-AmB (88% vs. 64%, $P = 0.014$). Additionally, survival rates were higher during induction with L-AmB (13% vs. 2%, $P = 0.04$).

The 2007 IDSA clinical practice guidelines for histoplasmosis recommend a lipid formulation amphotericin B for moderately severe to severe pulmonary (recommendation graded as "AIII") or disseminated (recommendation graded as "AI") disease and CNS infections (recommendation graded as "BIII").[40] The recommended L-AmB dose for pulmonary disease is 3 mg/kg/day for 1–2 weeks followed by a course of itraconazole for 12 weeks. The guidelines also recommend that CNS infections be treated with L-AmB 5 mg/kg/day for 4–6 weeks, followed by itraconazole for at least 12 weeks (recommendation graded as "B-III").

## Febrile neutropenia

Studies assessing the efficacy and safety of L-AmB for the empiric treatment of febrile neutropenia are summarized in Table 4. L-AmB has been compared to other amphotericin formulations, caspofungin and voriconazole in patients with febrile neutropenia. In a randomized trial of 687 patients with febrile neutropenia patients received L-AmB 3 mg/kg/day or AmBd 0.6 mg/kg/day until resolution of neutropenia. Overall treatment success (50.1% vs. 49.4%), fever resolution (58% vs. 58.1%), treatment of baseline fungal infection (81.8% vs. 72.7%), absence of

breakthrough fungal infection (90.1% vs. 89.2%), and survival at one week (92.7% vs. 89.5%) were similar between groups.[41] Another randomized trial in 244 neutropenic patients, compared two doses of L-AmB (3 or 5 mg/kg/day) to ABLC 5 mg/kg/day.[42] Patients were treated until recovery of neutrophils or a maximum of 42 days. Treatment success, a composite of symptomatic and mycologic parameters, was similar between the groups (40% vs. 42% vs. 33%). Persistence of baseline fungal infections (1.2% vs. 0% vs. 1.3%), emergent fungal infections (3.6% vs. 2.5% vs. 3.8%), and persistence of fever (40% vs. 29.6% vs. 26.9%) were also similar between groups.

Caspofugin 70 mg on day one followed by 50 mg daily was compared to L-AmB 3 mg/kg/day in a randomized trial of 1,095 febrile, neutropenic patients with persistent fever and neutropenia.[43] Treatment was continued for up to 3 days after neutrophil recovery. Caspofungin was demonstrated non-inferiority to L-AmB for the composite endpoint of overall success. The overall response rate was 33.7% for L-AmB and 33.9% for caspofungin (95% CI, −5.6 to 6.0). For patients with baseline fungal infections, a higher percentage had a successful outcome with caspofungin than with L-AmB (51.9% vs. 25.9%, $P = 0.04$). Survival at least seven days after therapy was 89.2% for L-AmB and 92.6% for caspofungin (95% CI, 0.0 to 6.8; $P = 0.05$). There were no significant differences in fever resolution and absence of breakthrough fungal infections between groups. Overall study mortality was higher with L-AmB (13.7%) than with caspofungin (10.8%) and a Kaplan-Meier analysis indicated the rate of survival after therapy was higher with caspofungin ($P = 0.04$).

Voriconazole 6 mg/kg loading dose, followed by 3 mg/kg twice daily was compared to L-AmB 3/mg/kg/day in a randomized trial of 837 febrile neutropenic patients.[44] Treatment was continued for up to 3 days after neutrophil recovery. Non-inferiority of voriconazole for the composite endpoint of overall success was not demonstrated. Response rates were 31% with L-AmB and 26% with voriconazole (95% CI, −10.6 to 1.6%). There were more breakthrough fungal infections with L-AmB (1.9% vs. 5%, $P = 0.02$) and survival at one week was similar between groups (92% vs. 94.1%; 95% CI −5.5 to 1.4%).

For efficacy assessments, these studies and many pivotal trials of empiric antifungal therapy employed a composite endpoint consisting of five equally weighted components. This composite endpoint has been criticized because it weights each of its components equally, when in fact each component may contribute differently to the overall success or failure of a given antifungal agent in a critically ill population.[45] Moreover, fever resolution is a component of the composite endpoint, which in critically ill neutropenic patients is a nonspecific endpoint that may not truly reflect antifungal efficacy.[45] A sensitivity analysis to determine the impact of varying definitions of fever resolution on response rates in a clinical trial of empirical antifungal demonstrated that requiring fever resolution during neutropenia can impact the analysis of clinical outcomes.[45] While fever resolution cannot be completely eliminated as a component of the composite endpoint analysis, these data suggest that modifications to this component are needed to improve the accuracy of efficacy assessments in future clinical trials of empirical antifungal therapy.[45]

## Mucormycosis

Lipid formulations of amphotericin have been suggested as the cornerstone of primary therapy for mucormycosis.[46] No prospective, randomized clinical trials have evaluated the efficacy of L-AmB in the treatment of mucormycosis. Compared to other invasive fungal infections, these infections occur less frequently and are often rapidly progressive in nature. For these reasons it is unlikely a large multicenter, appropriately controlled comparative trial will ever be performed. Therefore, the best available evidence comes in the form of case reports and case series. A review of 120 cases of mucormcycosis in patients with hematological malignancies reported a survival rate of 67% with L-AmB compared to 39% with AmBd ($P = 0.02$).[47] In 28 cases of mucormycosis treated with L-AmB, the overall mortality rate of patients receiving L-AmB as primary therapy was 61%. The response rate at the end of therapy was 32%. Doses ranged between 3 and 14 mg/kg/day, with most patients receiving 5–7.5 mg/kg/day.[48] In an analysis of 41 cases, L-AmB as initial antifungal therapy significantly improved the favorable response rate and survival when compared with other treatments. Doses ranged between 2 and 10 mg/kg/day, with an average of 5 mg/kg/day.[49]

## Safety

The safety and tolerability of L-AmB has been examined in randomized controlled trials. (Tables 1–4) Studies have evaluated the comparative rates of early treatment discontinuation due to toxicity, nephrotoxicity, infusion-related reactions, and electrolyte disturbances. When campared to other amphotericin formulations, discontinuation rates varied with dose and specific formulations. In general, standard dose L-AmB (3–5 mg/kg/day) is tolerated as well as AmBd and voriconazole; better than ABLC and high dose L-AmB, but not as well as certain echinocandins. In studies comparing standard dose L-AmB with AmBd, there was no difference in discontinuation rates observed.[37,41] However, higher discontinuation rates were observed with high dose L-AmB (>5 mg/kg/day) and ABLC when compared to standard dose L-AmB.[31,42]

When compared to micafungin, there was a trend towards more discontinuation due to toxicity with L-AmB in an adults and pediatric patients.[34,35] Higher rates of discontinuation due to adverse events were observed with standard dose L-AmB when compared to caspofungin.[43] No significant difference of discontinuation rates was observed when standard dose L-AmB was compared to voriconazole.[44]

### Nephrotoxicity

Nephrotoxicity is a common and serious toxicity associated with all amphotericin B formulations. Clinical trials have examined renal effects of L-AmB as compared to other amphotericin formulations, echinocandins, and voriconazole, with most studies defining nephrotoxicity as a doubling of serum creatinine. Standard dose L-AmB has consistently been shown to be less nephrotoxic than AmBd,[28,37,39,41] ABLC[42] and high dose L-AmB.[31] However, comparisons with echinocandins have produced differing results. In adults L-AmB was shown to cause more renal toxicity than caspofungin[43] or micafungin.[34] However, in pediatric populations there is little difference in the incidence of renal toxicity. Data in a pediatric patients comes from a sub-study of a larger comparative trial between L-AmB and micafungin[34] in which nephrotoxcity occurred in 3 patients, however in one patient it was attributed to the worsening of their underlying illness. Therefore, one patient who received L-AmB and one patient who received micafungin experienced nephrotoxicity that was attributed to their study medication.[35] As discussed previously, overall the incidence of adverse events that led to treatment discontinuation was lower in the micafungin group than in the liposomal amphotericin B group [3.8% (2/52) and 16.7% (9/54), respectively; $P = 0.05$, Fisher exact test].[35] Micafungin was discontinued in the patient who developed a moderate increase in serum creatinine, whereas in the patient receiving L-AmB, the renal dysfunction was not deemed severe enough to warrant drug discontinuation. The number of patients experiencing increases in serum creatinine to values greater than the upper limit of the normal reference range was identical (2 in each group).[35] No patient in either group experienced increases in serum creatinine greater than twice the upper limit of the normal reference range. However, L-AmB produced a greater reduction in the estimated glomerular filtration rate than micafungin (17.9 mL/min/1.73 $m^2$, N = 15 vs. 2.6 mL/min/1.73 $m^2$, N = 21, respectively).[35]

Overall, based upon the incidence of adverse events that led to treatment discontinuation, micafungin appears to have a safety advantage over L-AmB. However, these data suggest that in pediatric patients, while L-AmB is not devoid of nephrotoxic effects, severe reductions in renal function are rare. In a comparison with voriconazole, the standard dose L-AmB group had more cases of nephrotoxicity when defined as a serum creatinine greater than 1.5 times baseline. However, a difference was not observed when nephrotoxicity was defined as a doubling of serum creatinine.[44] The investigators noted that this result was consistent with the substantially lower nephrotoxicity of L-AmB compared to that of AmBd. They also noted that voriconazole was not associated with any increase in the frequency of renal abnormalities.[44]

Several issues regarding the nephrotoxicity of L-AmB formaulations have been debated including whether the individual formulations differ in their ability to cause this adverse effect, and whether it is related to dose. A recent meta analysis evaluated 8 studies (n = 1160) that evaluate the nephrotoxicity caused by either ABLC or L-AmB. Overall this analysis showed an increased probability of nephrotoxicity in patients treated with ABLC (n = 588) compared with those treated with L-AmB (n = 572).[50] However, in the analysis there was a lack of homogeneity and

the authors noted the overall results of the analysis should be interpreted cautiously.[50] Indeed the sensitivity analysis demonstrated that the results were highly influenced by a large prospective randomized comparative trial conducted by Wingard et al.[42] With the exception of that study the meta-analysis found no clinically relevant differences in nephrotoxicity between ABLC and L-AmB.[50]

Recent data have clarified the question of whether higher L-AmB doses are associated with an increased rates of nephrotoxicity than lower doses. In an early dose ranging study that assessed the safety of daily doses ranging from 7.5 mg/kg to 15 mg/kg one-half of patients had serum creatinine values that were ≥1.5 times greater than the baseline, and greater than 1.2 mg/dl at some point during the study.[51] Even when a higher nephrotoxicity threshold (≥2 times greater than the baseline) was applied, 32% of the population experienced this adverse effect.[51] The authors noted that there were no significant dosage-dependent trends observed for changes in serum creatinine levels.[51] Although no trends were noted, regardless of definition the lowest rates of nephrotoxicity were observed in the 7.5 mg/kg/day cohort and increased up to the 12.5 mg/kg/day cohort. With either threshold, the 15 mg/kg/day cohort produced nephrotoxicity rates that were slightly lower than the 12.5 mg/kg/day cohort, but yet were higher than the 7.5 mg/kg/day cohort.[51] Moreover, there were no cohorts that received less than 7.5 mg/kg/day to establish the nephrotoxicity rate of lower more standard dosages, therefore this study was not well designed to assess the dose-dependency of nephrotoxicity. Indeed, in studies of L-AmB using thresholds similar to the study of high-dose L-AmB, dosages ranging from 3–5 mg/kg/day have been associated with lower nephrotoxicity rates (ranging from 14.1%–28%).[50] In the most direct measure of the impact of dose on nephrotoxicity, a randomized trial comparing a high-loading dose (10 mg/kg/day) regimen with standard dosing (3 mg/kg/day) demonstrated significantly higher rates of nephrotoxicity (doubling of serum creatinine) in the high dose cohort compared to the standard dose cohort, 31% vs. 14%, respectively.[31]

## Infusion-related reactions

Infusion related reactions, primarily fever and chills or rigors, are another common toxicity of amphotericin formulations. In clinical trials, L-AmB was associated with fewer infusion-related reactions in comparisons with AmBd[37,39,41] and ABLC.[42] However, no difference in infusion related reactions was observed in a comparison of standard dose with high dose L-AmB.[31] In comparisons to echinocandins and voriconazole, higher rates of infusion-related reactions were observed with L-AmB.[34,43,44]

A clinical triad of severe acute infusion related reactions has been observed with L-AmB therapy. These reactions occur alone or in combination in one or more of three symptom complexes; 1) chest pain, dyspnea, and hypoxia 2) severe abdominal, flank or leg pain and 3) flushing and urticaria. The reactions typically occur within the first 5 minutes of infusion and can be treated by stopping the infusion and administering 1 mg/kg of diphenhydramine. Most patients will tolerate completion of the infusion and subsequent infusions with diphenhydramine premedication.[52]

## Conclusion

The liposomal composition of L-AmB slightly alters AmB pharmacokinetics in animals and humans. In certain animal infection models these subtle pharmacokinetic changes have enhanced the efficacy of the drug, but in humans they have not. Perhaps more importantly, incorporating AmB into a liposome or colloidal lipid complex alters the disposition and significantly improves the safety this drug in humans. Compared to AmB-d, the improved safety of L-AmB allows clinicians to use larger doses for longer treatment durations. Although compared to AmB-d larger doses can be employed, a true L-AmB dose-response relationship has not been established in many infections. Therefore, there are little if any data to suggest using higher than recommended L-AmB doses improves therapeutic outcomes. In fact the best available evidence in the treatment of invasive aspergillosis suggests doing so is counterproductive and may only increase the incidence adverse effects associated with L-AmB.

Evidence from well designed clinical trials, supports the use of L-AmB against a variety of pathogenic yeast and moulds. In general, with the exception of invasisive aspergillosis, in widely accepted guidelines, L-AmB is listed among the choices for primary (ie, “first-line”) therapy of common invasive

fungal infections including various forms of Candidiasis, Cryptococcosis, and Histoplasmosis in immunocompromised or immunosuppressed patients. With the exception of Histoplasmosis, in widely accepted guidelines, L-AmB is often considered an alternative agent to other effective therapies for the treatment of common invasive fungal infections including various forms of Candidiasis, and Cryptococcosis in non-neutropenic patients. L-AmB has demonstrated similar efficacy as other amphotericin formulations and caspofungin for empiric therapy in patients with febrile neutropenia. However, improved efficacy measurements are needed to more accurately assess the benefit of a given antifungal agent in this setting. Moreover, revised guidelines are needed to inform current practice. Data from case series support the use of L-AmB in the treatment of mucormycosis.

With standard doses L-AmB is better tolerated than other amphotericin formulations and produces less nephrotoxicity than AmB-d. However, like other lipid formulations, L-AmB is not devoid of nephrotoxic effects. Therefore, nephrotoxicity rates associated with L-AmB increase with dose. Furthermore, when compared to other therapies including the echinocandins, nephrotoxicity is more common with L-AmB, particularly in adults. Collectively, the data demonstrate that by improving the safety of AmB, and maintaining its efficacy, L-AmB is an effective and valuable agent in the antifungal arsenal to treat invasive fungal infections.

## Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

## References


1. Goodwin SD, Cleary JD, Walawander CA, Taylor JW, Grasela TH Jr. Pretreatment regimens for adverse events related to infusion of amphotericin B. *Clin Infect Dis*. 1995;20:755–61.
2. New RCC, Chance ML, Heath S. Antileishmanial activity of amphotericin and other antifungal agents entrapped in liposomes. *J Antimicrob Chemother*. 1981;8:371–81.
3. Graybill JR, Craven PC, Taylor RL, Williams DM, Magee WE. Treatment of murine cryptococcosis with liposome-associated amphotericin B. *J Infect Dis*. 1982;145:748–52.
4. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. *J Molecular Biol*. 1965;13:238–52.
5. Fielding RM. Liposomal drug delivery: advantages and limitations from a clinical pharmacokinetic and therapeutic perspective. *Clin Pharmacokinet*. 1991;21:155–64.
6. Adler-Moore J, Proffitt RT. Ambisome: liposomal formulation, structure, mechanism of action and pre-clinical experience. *J Antimicrob Chemother*. 2002;49 Suppl S1:21–30.
7. Maurer N, Fenske DB, Cullis PR. Developments in liposomal drug delivery systems. *Expert Opin Biol Ther*. 2001;1:923–47.
8. Bloom M, Evans E, Mouritsen OG. Physical properties of the fluid lipid-bilayer component of cell membranes: a perspective. *Quart Rev Biophys*. 1991;24:293–397.
9. Adler-Moore J, Proffitt RT. Development, characterization, efficacy and mode of action of AmBisome, a unilamellar liposomal formulation of amphotericin B. *J Liposome Res*. 1993;3:429–50.
10. Kirby C, Clarke J, Gregoriadis G. Effect of cholesterol content of small unilamellar lioposomes on their stability in vivo and in vitro. *Biochem J*. 1980;186:591–8.
11. Brajtburg J, Bolard J. Carrier effects on biological activity of amphotericin B. *Clin Microbiol Rev*. 1996;9:512–31.
12. Semple SC, Chonn A, Cullis PR. Interactions of liposomes and lipid-based carrier systems with blood proteins: relation to clearance behaviour in vivo. *Adv Drug Del Rev*. 1998;32:3–18.
13. Gabizon A, Papahadjopoulos D. The role of surface charge and hydrophilic groups on liposomal clearance in vivo. *Biochem Biophys Acta*. 1992;1103:94–100.
14. Karlowsky JA, Zhanel GG. Concepts on the use of liposomal antimicrobial agents: applications for aminoglycosides. *Clin Infect Dis*. 1992;15:654–7.
15. Janknegt R, de Marie S, Bakker-Woudenberg I, Crommelin DJA. Liposomal and lipid formulations of amphotericin B: clinical pharmacokinetics. *Clin Pharmacokinet*. 1992;23:279–91.
16. Bekersky I, Fielding RM, Dressler DE, Lee JW, Buell DN, Walsh TJ. Plasma protein binding of amphotericin B and pharmacokinetics of bound versus unbound amphotericin B after administration of intravenous liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate. *Antimicrob Agents Chemother*. 2002;46:834–40.
17. Boswell GW, Buell D, Bekersky I. Ambisome (liposomal amphotericin B: a comparative review. *J Clin Pharmacol*. 1998;38:583–92.
18. Bekersky I, Fielding RM, Dressler DE, Lee JW, Buell DN, Walsh TJ. Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate in humans. *Antimicrob Agents Chemother*. 2002;46:828–33.
19. Fielding RM. Relationship of pharmacokinetically-calculated volumes of distribution to the physiologic distribution of liposomal drugs in tissues: implications for the characterization of liposomal formulations. *Pharm Res*. 2001;18:238–42.
20. Vogelsinger H, Weiler S, Djanani A, et al. Amphotericin B tissue distribution in autopsy material after treatment with liposomal amphotericin B and amphotericin B colloidal dispersion. *J Antimicrob Chemother*. 2006; 57:1153–60.
21. Groll AH, Lyman CA, Petraitis V, et al. Compartmentalized intrapulmonary pharmacokinetics of amphotericin B and its lipid formulations. *Antimicrob Agents Chemother*. 2006;50:3418–23.
22. Groll AH, Giri N, Petraitis V, et al. Comparative efficacy and distribution of lipid formulations of amphotericin B in experimental Candida albicans infection of the central nervous system. *J Infect Dis*. 2000;182:274.
23. Leenders A, Reiss P, Portegies P, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. *AIDS*. 1997;11:1463–71.
24. Groll AH, Mickiene D, Piscitelli SC, Walsh TJ. Distribution of lipid formulations of amphotericin B into bone marrow and fat tissue in rabbits. *Antimicrob Agents Chemother*. 2000;44:408–10.
25. Mouton JW, Theuretzbacher U, Craig WA, et al. Tissue concentrations: do we ever learn? *J Antimicrob Chemother*. 2008;61(2):235–7.
26. Müller M, dela Pena A, Derendorf H. Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: distribution in tissue. *Antimicrob Agents Chemother*. 2004;48(5):1441–53.

27. Kiem S, Schentag JJ. Interpretation of antibiotic concentration ratios measured in epithelial lining fluid. *Antimicrob Agents Chemother*. 2008; 52(1):24–36.
28. Leenders AC, Daenen S, Jansen RL, et al. Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. *Br J Haematol*. 1998;103:205–12.
29. Ellis M, Spence D, de Pauw B, et al. An EORTC international multicenter randomized trial (EORTC number 19923) comparing two dosages of liposomal amphotericin B for treatment of invasive aspergillosis. *Clin Infect Dis*. 1998;27(6):1406–12.
30. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;46(3):327–60.
31. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Infect Dis*. 2007;44(10):1289–97.
32. Perfect JR. Nuances of new anti-*Aspergillus* antifungals. *Med Mycol*. 2005;43 Suppl 1:S271–6.
33. Caillot D, Thiébaut A, Herbrecht R, et al. Liposomal amphotericin B in combination with caspofungin for invasive aspergillosis in patients with hematologic malignancies: a randomized pilot study (Combistrat trial). *Cancer*. 2007;110(12):2740–6.
34. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. *Lancet*. 2007;369(9572):1519–27.
35. Queiroz-Telles F, Berezin E, Leverger G, et al. Micafungin versus liposomal amphotericin B for pediatric patients with invasive candidiasis: substudy of a randomized double-blind trial. *Pediatr Infect Dis J*. 2008;27(9):820–6.
36. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(5):503–35.
37. Hamill RJ, Sobel JD, El-Sadr W, et al. Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety. *Clin Infect Dis*. 2010;51(2):225–32.
38. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(3):291–322.
39. Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Ann Intern Med*. 2002;137(2):105–9.
40. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45(7):807–25.
41. Walsh TJ, Finberg RW, Arndt C, Hiemenz J, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med*. 1999;340(10):764–71.
42. Wingard JR, White MH, Anaissie E, et al. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. *Clin Infect Dis*. 2000;31(5):1155–63.
43. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med*. 2004;351(14):1391–402.
44. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med*. 2002;346(4):225–34.
45. de Pauw BE, Sable CA, Walsh TJ, et al. Impact of alternate definitions of fever resolution on the composite endpoint in clinical trials of empirical antifungal therapy for neutropenic patients with persistent fever: analysis of results from the Caspofungin Empirical Therapy Study. *Transpl Infect Dis*. 2006;8:31–7.
46. Spellberg B, Walsh TJ, Kontoyiannis DP, et al. Recent advances in the management of mucormycosis: from bench to bedside. *Clin Infect Dis*. 2009;48:1743–51.
47. Gleissner B, Schilling A, Anagnostopolous I, et al. Improved outcome of zygomycosis in patients with hematological diseases? *Leuk Lymphoma*. 2004;45(7):1351–60.
48. Shoham S, Magill SS, Merz WG, et al. Primary treatment of zygomycosis with liposomal amphotericin B: analysis of 28 cases. *Med Mycol*. 2010;48(3):511–7.
49. Rüping MJ, Heinz WJ, Kindo AJ, et al. Forty-one recent cases of invasive zygomycosis from a global clinical registry. *J Antimicrob Chemother*. 2010;65(2):296–302.
50. Safdar A, Ma J, Saliba F, et al. Drug-induced nephrotoxicity caused by amphotericin B lipid complex and liposomal amphotericin B: a review and meta-analysis. *Medicine*. 2010;89(4):236–244.
51. Walsh TJ, Goodman JL, Pappas P, et al. Safety, tolerance, and pharmacokinetics of high-dose liposomal amphotericin B (AmBisome) in patients infected with *Aspergillus* species and other filamentous fungi: maximum tolerated dose study. *Antimicrob Agents Chemother*. 2001;45(12):3487–96.
52. Roden MM, Nelson LD, Knudsen TA, et al. Triad of acute infusion-related reactions associated with liposomal amphotericin B: analysis of clinical and epidemiological characteristics. *Clin Infect Dis*. 2003;36(10):1213–20.