Does evidence support high-dose liposomal amphotericin B in the treatment of mucormycosis?

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Abstract

Introduction: Invasive mucormycosis is a life-threatening fungal infection with mortality rates of 40-80%. Current guidelines recommend liposomal amphotericin B (L-AMB) as first-line therapy with a broad dosing range of 5-10 mg/kg/day, but uncertainty persists regarding whether higher doses improve outcomes given the substantial nephrotoxicity risks and increased costs associated with dose escalation. Areas covered: This review critically evaluates pharmacokinetic, preclinical, and clinical evidence supporting high-dose L-AMB therapy for mucormycosis. We examine the concentration-dependent pharmacodynamics of amphotericin B, review animal model studies demonstrating dose-response relationships, and analyze the non-linear pharmacokinetics observed in humans, where plasma drug concentrations plateau at 10 mg/kg/day and paradoxically decline at higher doses. We summarize findings from the prospective AmBizygo pilot trial and recent observational studies from Japan and the United States comparing standard-dose (5-6 mg/kg/day) versus high-dose (≥6 mg/kg/day) L-AMB regimens. Literature searches were conducted through December 2024 using PubMed and conference proceedings.Expert opinion: Current clinical evidence does not support routine use of high-dose L-AMB for mucormycosis. Despite clear dose-response relationships in animal models, observational studies consistently demonstrate no survival benefit with doses exceeding 5-6 mg/kg/day, while nephrotoxicity increases. Clinicians should prioritize standard dosing (5-6 mg/kg/day), reserving escalation for specific situations such as CNS involvement. Future research should focus on therapeutic drug monitoring strategies, identifying patient subgroups with suboptimal drug exposure, novel combination regimens, and host-directed immunotherapies rather than empiric dose escalation. Surgical debridement and immune recovery remain more strongly associated with survival than antifungal dosing intensity.

# Introduction

Invasive mucormycosis, caused primarily by *Rhizopus, Mucor, and Lichtheimia* species of the order Mucorales, is a life-threatening fungal infection that has increased in incidence over the past two decades, predominantly affecting immunocompromised patients with hematologic malignancies, solid organ or hematopoietic cell transplantation, and poorly controlled diabetes mellitus [1]. Characterized by aggressive angioinvasion and tissue necrosis, mucormycosis carries mortality rates of 40-80% depending on infection site, diagnostic and treatment delays, feasibility of surgical debridement, and host immune recovery [2–5]. Current guidelines recommend initial therapy with intravenous liposomal amphotericin B (L-AMB) until clinical stabilization, followed by step-down to posaconazole or isavuconazole [6,7].

Due to the aggressiveness of the infection, higher L-AMB doses (>5 mg/kg/day) are frequently recommended during the acute treatment phase of infection to rapidly load infected tissue to limit fungal invasion and dissemination [8,9]. While experimental animal models demonstrate a clear dose-response relationship for L-AMB [10],  prospective trials [11,12] and observational studies [13–15] have not confirmed improved outcomes with higher L-AMB dosing. Indeed, the *Global Guidelines for the Diagnosis and Management of Mucormycosis* developed by the European Confederation of Medical Mycology (ECMM)/Mycoses Study Group Education and Research Consortium (MSGERC) recommend a broad initial dosing range for liposomal amphotericin B of 5-10 mg/kg/day [16].

Uncertainty regarding the optimal dosing of L-AMB is clinically important as higher doses often carry increased risks of nephrotoxicity and infusion-related as well as higher drug costs [17]. In this review, we critically evaluate the pharmacokinetic, preclinical, and clinical evidence supporting dose escalation, examine patient-specific factors that may influence the benefit-risk ratio of high-dose L-AMB therapy for mucormycosis, and provide practical recommendations for individualizing dosing of this essential antifungal medication.

# Pharmacodynamics of liposomal amphotericin B

Amphotericin B (AMB) is a polyene macrolide antifungal agent with broad-spectrum activity against most clinically relevant fungi. Its amphiphilic structure renders it insoluble in body fluids at a neutral pH. The primary mechanism of antifungal action has long thought to involve binding to ergosterol in fungal cell membranes, forming transmembrane channels that disrupt membrane integrity and cause lethal ion leakage, particularly of potassium. However, more recent studies using solid-state NMR suggest amphotericin B forms extramembrane aggregates or “sponges” that extract ergosterol from the fungal cell wall [18,19]. When incorporated into a liposome, the polyene remains inside the liposome carrier until drug is released when the liposome comes in contact with ergosterol in teh fungal cell membrane[20].

Clinical use of liposomal formulation is associated with fewer delayed (2-6 hour) infusion-related reactions mediated by proinflamamtory cytokine (e.g., Interleukin (IL-1ß, IL-6, IL-8 and prostaglandin E2) release. However, an immediate unique type-1 hypersensitivity reaction termed “complement activation-related pseudoallergy” (CARPA) can develop within minutes of L-AMB infusion characterized by a triad of symptoms including: (1) chest pain, dyspnea, hypoxia; (2) abdominal, flank, or leg pain; and (3) flushing and urticaria [21]. Amphotericin B-associated nephrotoxicity, which arises through direct constriction of renal arterioles and direct damage to the distal tubular membranes resulting in loss of potassium and bicarbonate, is reduced with the liposomal formulation due to the preferential distribution of the drug to organs rich in reticuloendothelial cells and lack of glomerular filtration of the liposome carrier [22].

Amphotericin B exhibits concentration-dependent killing and prolonged post-antifungal effects in yeast and molds, with antifungal effects linked to the Cmax/MIC and AUC0-24/MIC- thus supporting the concept that  higher, infrequently administered dosing regimens will exhibit better antifungal efficacy [23–25]. In neutropenic and rabbit models of aspergillosis, near-maximal antifungal efficacy is observed when the total serum amphotericin B concentrations Cmax/MIC surpasses 2.5 or and AUC0-24/MIC of 13.6 [26]. However, encapsulation of amphotericin B in the unilamellar liposomes changes the pharmacokinetics and pharmacodynamics of the drug, reducing drug interactions with mammalian cell membranes while enhancing tissue distribution and reducing toxicity compared with conventional amphotericin B deoxycholate [27]. Hence, the liposome carrier confounds the PK/PD relationship between serum drug concentrations, which contain both non biologically active drug encased inside liposomes and free drug, versus biological activity observed in infected tissue.

Few studies have explored the pharmacodynamics of escalating L-AMB doses in animal models of mucormycosis. Using a neutropenic mouse model of pulmonary mucormycosis, Lewis et al. [28] reported improved clearance of *R. oryzae* lung fungal burden as daily intravenous doses of L-AMB increased from 5 mg/kg to 10 mg/kg daily. Fungal clearance correlated with lung tissue homogenate concentrations of AMB surpassing the mean fungicidal concentration (MFC) of the *R. oryzae* isolate (8 mg/L) inoculated in animals. Interestingly, total lung concentrations of amphotericin B decreased after 72 hours as fungal burden declined despite sustained 10 mg/kg/day dosing, suggesting either saturation of drug accumulation in the lung or decreased distribution of the liposomes to the lung with fungal clearance.

Studies using diabetic ketoacidosis and pulmonary mucormycosis infection models by the Ibrahim research group at UCLA [29–32] and Takemoto et al. [33] confirmed that L-AMB doses ≥10 mg/kg/day achieve superior tissue fungal clearance compared to lower doses, particularly in the central nervous system. In a review of L-AMB tissue penetration data from animal models, Adler-Moore et al. confirmed  accumulation of L-AMB increases in a dose-dependent manner [34]. However, the dose-response relationship varies by organ, exhibiting linear kinetics in some tissues and non-linear kinetics in others, influenced by both animal species and infection status. The liver and spleen consistently show the highest drug retention across all animal infection models.

# Human pharmacokinetics

Following intravenous administration, liposomal amphotericin B (L-AMB) maintains its physicochemical integrity over extended periods, resulting in prolonged residence time within the central compartment [Figure 1](#fig-distribution).

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| Figure 1: Pharmacokinetic model of liposomal amphotericin B. Following intravenous administration, liposomal amphotericin B distributes from the central compartment (1, plasma) to reticuloendothelial system organs including the liver, spleen, and bone marrow (compartment 2), and to kidney, lung and other peripheral tissues (compartment 3). Rate constants (*k*) indicate bidirectional transfer between compartments: *k12* and *k21* represent distribution and redistribution between plasma and reticuloendothelial organs; *k13* and *k31* between plasma and peripheral tissues; and *k23* and *k32* between reticuloendothelial organs and peripheral tissues. Drug elimination occurs from the central compartment via biliary and urinary excretion (dotted arrow). Figure adapted from Groll et al [35]. |

The drug exhibits non-linear pharmacokinetics with substantial interpatient pharmacokinetic variability across therapeutic doses. At doses of 1.0, 2.5, 5.0, and 7.5 mg/kg, first-day mean AUCs increased disproportionally (32, 71, 294, and 534 µg·h/mL, respectively) [Table 1](#tbl-pk). Concurrently, mean plasma clearance declined at higher doses, decreasing from 39-51 mL/h/kg at 1.0-2.5 mg/kg/day to 21-25 mL/h/kg at 5.0-7.5 mg/kg/day [36].

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| Table 1: Pharmacokinetic and pharmacodynamic properties of liposomal amphotericin B. aData are from reference [37] ; bData are from reference [38] ; c Data are from reference [39]   | Characteristic |  | | --- | --- | | Formulation | Small (60-80 nm) unilamellar liposomes consisting of distearoyl phosphatidylglycerol, cholesterol, and hydrogenated soy phosphatidylcholine; in a 2:1:0.8 molar ratio and AmB in a 9:1 lipid:drug molar ratio | | Pharmacodynamics | Cmax/MIC, AUC/MIC | | Free (non-liposomal bound drug) in plasmaa | <25 ng/mL | | Mean Cmax mg/Lb | 58 | | Mean AUC0-24h mg/Lxhb | 713 | | Mean CLt L/h/kgb | 0.017 | | Dose linearityc | Up to 10 mg/kg/day in adults | | Metabolism | Not metabolized | | Elimination | Unchanged feces and urine (< 10% over one week) | | Dosage adjustment in renal impairment | No adjustment for accumulation concerns | | Dosage adjustment in hepatic impairment | No adjustment for accumulation concerns | |

This non-linear behaviour becomes more pronounced with further dose escalation. A subsequent Phase I/II trial evaluating 10, 12.5, and 15 mg/kg/day L-AMB in patients with invasive mold infections reported mean AUC and Cmax values plateaued at 10 mg/kg/day and paradoxically declined at doses of 12.5 and 15 mg/kg/day, indicating saturable distribution or elimination pathways [40]. Therefore, it is unclear whether L-AMB daily dosages exceeding 10 mg/kg distribute more drug to target organs such as the lung, sinuses or brain, which are the most frequent sites of infection in invasive mucormycosis.

# Clinical studies

Several observational studies and one prospective pilot study evaluated clinical outcomes follwing administration of HD L-AMB [Table 2](#tbl-clinical). The most informative trial to date has been the AmBizygo trial lead by Lanternier et al, which prospectively evaluated high-dose liposomal amphotericin B (10 mg/kg/day) for 4 weeks in 34 patients with mucormycosis, with 71% undergoing surgical debridement [41]. The overall response rate was 36% at week 4 and 45% at week 12, with mortality rates of 38% and 53% at weeks 12 and 24, respectively. Creatinine doubling occurred in 40% of patients, though renal dysfunction was reversible in 63% within 3 months. This study demonstrated that high-dose L-AMB combined with surgery achieved response rates comparable to or better than other first-line therapies, despite increased but manageable nephrotoxicity.

Although not specific for mucormycosis, the AmBiLoad trial was a randomized, double-blind study of 201 patients with invasive mold infections (97% aspergillosis) comparing liposomal amphotericin B at 3 mg/kg/day versus 10 mg/kg/day for 14 days followed by 3 mg/kg/day [42]. No significant differences in favorable response (50% vs 46%) or 12-week survival (72% vs 59%) were observed between standard and high-dose groups, while nephrotoxicity (14% vs 31%, P<0.01) and grade 3 hypokalemia (16% vs 30%, P=0.015) were significantly higher in the high-dose group. The trial established that 3 mg/kg/day liposomal amphotericin B is effective for invasive aspergillosis with no additional benefit from dose escalation to 10 mg/kg/day.

Retrospective observational studies of invasive mucormycosis have generally failed to identify a signal of improved outcomes for patients treated with higher versus standard doses of L-AMB [Table 2](#tbl-clinical). However, interpretation of patient outcomes is confounded by unstandardized diagnosis, frequent use or combination therapy and surgical resection, and differences in host immunosuppression and underlying disease status.

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| Table 2: Clinical studies evaluting high-dose liposomal amphotericin B for mucormycosis   | Author- year | Study design | L-AMB treatment regimen | Outcomes | | --- | --- | --- | --- | | Lanternier et al. 2015 [43] | Prospective, multicenter pilot study; n=40 patients;most hematologic malignancy, 33% neutropenic | 10 mg/kg/day for median of 13.5 days (range 0-28) | Response rate (n=33 patients at week 4) 38% overall mortality at week 12 and 53% at week 24 SeCr doubling in 40% of patients | | Valiante et al. 2023 [44] | Retrospective cohort study; (n=67 adults with probable/proven mucormycosis | L-AMB < 6 mg/kg/dayvs. ≥ 6 mg/kg/day | 12-week mortality rate 49 vs. 50% Similar rates of acute kidney injury (47% v.s 50%) | | Tashiro et al. 2023 [45] | Retrospective multicenter nationwide cohort analysis n=82 cases | L-AMB 5 mg/kg/day vs. ≥ 5 mg/kg/day | No difference in survival between patients receiving liposomal amphotericin B at 5 mg/kg/d relative to those receiving >5 mg/kg/d (P = .625). In analysis adjusting for confounders, the hazard ratio for the influence of >5 mg/kg/d liposomal amphotericin B on 4-week survival was 0.86 (95% CI, 0.28–2.68; P = .796) compared with 5 mg/kg/d. | | Stover et al. 2024 [46] | Single-center case series, mixed population | L-AMB mean 8.9 mg/kg/day for 11 days | Response rate 33% one-third of patients developed doubling baseline serum creatine | | Jeong et al. 2019 [47] | Systematic review of 851 published cases, mixed population | n=57 received high-dose L-AMB (6–15 mg/kg/day) | Patients receiving L-AmB doses at > 5 mg/kg/day experienced higher 90-day mortality, although not statistically significant [22/57 (38.6%) vs. 29/93 (31.2%); P = 0.352]. In addition, renal toxicity was more common following administration of higher-dose i.v. L-AmB [15/57 (26.3%) vs. 12/93 (12.9%); P = 0.038 | | Elitzuer et al. 2021 [48] | Retrospective analysis of 12 pediatric cases, mixed posultion | N=5/12 (42%) received HD L-AMB during treatment only 1/5 (20%) as monotherapy | 4/5 (80%) of patients survived with HD L-AMB vs. 4/5 died with standard dose of L-AMB (3/5 in combination with triazole or echinocandin) | | Risum et al. 2020 [49] | Retrospective analysis of 13 patients with invasive mucormycosis | 3/13 received HD L-AMB for suspected CNS involvement in combination with other antifungals | 3/3 response (100%) with HD-L-AMB vs. 10/13 standard dose (77%) | |

# Future implications

Collectively, the clinical evidence does not provide strong evidence that higher-dose (>5-6 mg/kg/day) L-AMB improves outcomes for mucormycosis. While preclinical models demonstrate dose-dependent efficacy, observational studies and the AmBizygo pilot trial have failed to demonstrate improved survival with dose escalation beyond 5 mg/kg/day, despite increased nephrotoxicity risks. Several key knowledge gaps must be addressed to optimize L-AMB dosing strategies for this devastating infection.

First, the non-linear pharmacokinetics and apparent plateau in tissue distribution at doses exceeding 10 mg/kg/day warrant further investigation through prospective pharmacokinetic studies with tissue sampling. Understanding whether higher doses actually deliver more biologically active amphotericin B to target sites such as lungs, sinuses, and brain—the most common sites of mucormycosis—is critical. Studies measuring free (non-liposome encapsulated) amphotericin B concentrations in infected tissues, rather than total drug concentrations, would provide more relevant pharmacodynamic targets. Moreover, identifying patient subgroups who achieve suboptimal drug exposure at standard doses—potentially due to high body weight, critical illness, or extracorporeal membrane oxygenation—may reveal populations who could benefit from dose escalation.

Third, prospective randomized controlled trials comparing standard (5 mg/kg/day) versus high-dose (10 mg/kg/day) L-AMB remain the gold standard for establishing optimal dosing but face significant feasibility challenges given the rarity of mucormycosis. Collaborative international registry studies with standardized treatment protocols and detailed pharmacokinetic sampling could provide valuable real-world evidence. Such studies should stratify patients by infection site (particularly CNS involvement, where higher doses are commonly recommended), underlying immunosuppression, and timing of surgical debridement to identify patient-specific factors that modify the dose-response relationship.

Fourth, the observational studies reviewed demonstrate that surgical debridement is more strongly associated with survival than antifungal dosing regimen- although confounding by indication bias may overestimate the benfits of surgery in these analysis. Future research should focus on integrated treatment strategies that optimize the synergy between surgical source control and antifungal therapy. Studies examining whether dose escalation specifically benefits patients with unresectable disease or delayed surgical intervention would address a clinically relevant question.

Fifth, novel amphotericin B formulations or combination regimens may overcome the limitations of current L-AMB dosing. Although recent observational studies have not found a major benefit for combinations of L-AMB with echinocandins or triazoles in muycormycosis [50], animal models have demonstrated improved survival and fungal clearance when L-AMB is combined with isavuconazole [51] , the glucan synthesis inhibitor ibrexafungerp [52] , and the (GPI)-anchor biosynthesis pathway inhibitor manogepix [53]. Additionally, host-directed therapies that block fungal invasion through CotH [54] proteins or neutralize mycotoxins [55] should be explored as adjuncts to standard-dose antifungal therapy. Novel Immunotherapuetic approaches including checkpoint inhibitor therapy [56] or chimeric antigen T- cell approaches could be effective “living antifungals”[57] after initial treatment with L-AMB. Finally, economic analyses comparing the costs of high-dose L-AMB therapy (including management of nephrotoxicity and potential renal replacement therapy) against marginal clinical benefits are needed to inform rational resource allocation, particularly in resource-limited settings where mucormycosis incidence may be highest.

Based on current evidence, clinicians should consider 5-6 mg/kg/day as an appropriate initial L-AMB dose for most patients with mucormycosis, with dose escalation reserved for selected situations where compelling clinical rationale exists (such as CNS involvement or suspected suboptimal drug exposure) and close monitoring of renal function is feasible. Treatment decisions should prioritize early diagnosis, prompt surgical debridement when feasible, and reversal of underlying immunosuppression over empiric dose escalation. Future research must move beyond simple dose-response paradigms to embrace personalized, exposure-guided dosing strategies informed by robust pharmacokinetic-pharmacodynamic relationships and patient-specific risk factors.

# Plain language summary

Mucormycosis is a rare but deadly fungal infection primarily affecting immunocompromised patients that is treated with surgery and an antifungal medication called liposomal amphotericin B, with ongoing debate about whether higher drug doses improve survival despite increased kidney damage risks. While laboratory studies in mice demonstrated that higher doses killed more fungus in infected tissues, multiple recent clinical studies in humans found no survival difference between patients receiving standard doses (5 mg/kg/day) versus higher doses (6-15 mg/kg/day), and the drug’s complex behavior in the body means extra doses may not actually reach infected tissues effectively. Based on current evidence, doctors should use standard doses for most patients and focus instead on rapid diagnosis, surgical removal of infected tissue, and helping patients’ immune systems recover, as these factors are more strongly associated with survival than higher antifungal doses.

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