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

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Abstract

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# 1. 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 amphot[6]ericin B (L-AMB) until clinical stabilization, followed by step-down to posaconazole or isavuconazole [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]. While experimental animal models demonstrate a clear dose-response relationship for L-AMB [9],  prospective trials [10,11] and observational studies [12–14] 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 [15].

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 [16]. 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.

# 2. 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 [17,18]. 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[19].

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, although an immediate unique type-1 hypersensitivity reaction termed “complement activation-related pseudoallergy” (CARPA) can arise from infusion of the liposomes [20]. 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 [21].

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 [22–24]. 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 [25]. 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 [26]. 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. [27] 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 [28–31] and Takemoto et al. [32] 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 [33]. 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.

# 3. Pharmacokinetics in Patients

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 [34]. |

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 [35].

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| Table 1: Pharmacokinetic and pharmacodynamic properties of liposomal amphotericin B.   | 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 | | aData are from reference [36] ; bData are from reference [37] ; c Data are from reference [38] |  | |

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 [39]. 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.

# 4. Clinical studies

Several observational studies and two small randomized trials have evaluated clinical outcomes follwing administration of HD L-AMB [Table 2](#tbl-clinical).

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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 [40] | 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[41] | 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[42] | Retrospective multicenter nationwide cohort analysis n=82 cases | L-AMB 5 mg/kg/day vs. ≥ 5 mg/kg/day | Survival did not differ between patients receiving liposomal amphotericin B at 5 mg/kg/d relative to those receiving >5 mg/kg/d (P = .625). Using Cox proportional hazards models and 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 [43] | Single-center case series | 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 [44] | Systematic review of 851 published cases | n=57 received high-dose L-AMB (6–15 mg/kg/day) | Compared with patients receiving 5 mg/kg/day of i.v. L-AmB, those who received higher doses had a 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 | | Spellberg et al. |  |  |  | |

# 5. Future implications

# 6. Plain language summary

# 7. References

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