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REVIEW

High-dose amphotericin: yay or nay? A case series and literature review

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Abstract

Invasive fungal infections pose significant morbidity and mortality risks, particularly those caused by moulds. Available antifungal classes are limited by toxicities and are increasingly susceptible to resistance, particularly amongst challenging fungal pathogens. The purpose of this case series and literature review was to characterize the use of a high-dose lipid formulation of amphotericin B. A case series is presented including patients who received high-dose lipid formulation amphotericin B (≥7.5 mg/kg/day) between June 2012 and August 2021. Additionally, a systematic literature review was conducted by searching the PubMed database for English-language studies involving individuals who received high-dose amphotericin B therapy (≥7.5 mg/kg) using lipid formulations. Nine patients were included in the case series, receiving an average of 8.9 ± 1.3 mg/kg liposomal amphotericin B over a mean of 11.0 ± 10.8 days predominantly for mould infections including Mucorales, aspergillosis and *Fusarium*. The patients were primarily cared for in intensive care units, with varying treatment histories and outcomes. A total of 11 studies (*n*=260 patients) met inclusion criteria for the literature review. Responses to high-dose liposomal amphotericin B ranged from 8% to 100%, often showing favourable outcomes. High doses of liposomal amphotericin B were well tolerated both in the case series and in published literature, with serum creatinine changes being the most commonly reported adverse event. However, multi-patient studies continue to report less than favourable (range 8–62%) response rates. High-dose liposomal amphotericin B, either alone or in combination with other antifungal agents, might be a viable strategy for managing invasive fungal infections when few treatment choices exist.

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Introduction

Invasive fungal infections are responsible for high rates of morbidity and mortality.[1,2] Although *Candida* species are associated with a long list of risk factors, the primary risk factor for infections with *Cryptococcus* species, dimorphic fungi and moulds is immunosuppression.[3,4] Although the prevalence of mould infections has historically been low, increasing incidence has been seen as a result of more frequent use of broad-spectrum antifungal prophylaxis, increasing use of therapeutic immunosuppression (e.g. use of prolonged corticosteroids, chemotherapy or immunosuppressant agents), and increasingly intensive antimicrobial treatment of patients hospitalized with infections.[5]

Therapy choices for invasive fungal infections have been relatively limited, especially when compared with antibacterial options. Azole antifungals, widely variable in spectrum across agents, are associated with drug–drug interactions,

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hepatic toxicity and QT prolongation. The echinocandins, whilst relatively well tolerated, are narrow in spectrum with coverage for *Candida* species and limited moulds only. Flucytosine is limited by haematological and renal toxicity. Amphotericin B provides broad-spectrum coverage but is limited by its historical reputation for high incidences of renal toxicity, cardiac toxicity and infusion reactions. Furthermore, all classes of antifungals are increasingly affected by the development of resistance, especially for these more difficult-to-treat fungal pathogens.[6]

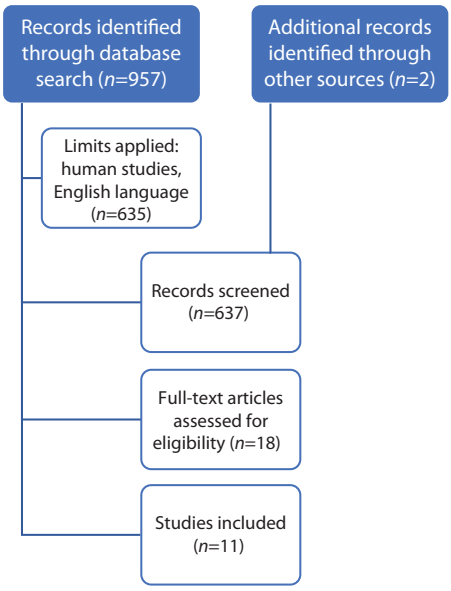
Improvements in some of these toxicities have occurred with the increasing use of lipid formulations of amphotericin B. Manufacturer labelling recommends doses of 2.5–5 mg/kg, and routine clinical doses have increased within that range (e.g. historical use of 2.5 mg/kg with a slow increase to 5 mg/kg routinely over time) since approval.[7–13] In recent years, the lack of response of some infections to standard doses of amphotericin B have pushed the dosing boundaries of this drug, resulting in clinical use of higher-than-approved doses. The purpose of this case series and literature review is to characterize high-dose lipid formulation amphotericin B use and describe the therapeutic effects of high-dose lipid formulations of amphotericin B on patients at one institution and in the literature.

Methodology

For the case series, patients admitted to the University of Mississippi Medical Center between June 2012 and August 2021 who received high-dose lipid complex or liposomal amphotericin, defined as daily receipt of ≥7.5 mg/kg/day, were included. Amphotericin dosing at this institution is at the discretion of the provider, and there is no formal protocol or guidelines for use. Most patients included in this retrospective case series were escalated to higher-than-standard doses based on severity of infection or lack of therapeutic response. This case series was approved by the Institutional Review Boards at the University of Mississippi Medical Center and University of Mississippi School of Pharmacy. All patient information was deidentified, and patient consent was not required. Favourable response was defined as having no inpatient mortality, no infection-related readmission within 90 days and no repeated cultures positive for the same organism within 6 months.

A systematic search of PubMed was performed with the search terms "amphotericin B" and "high dose" (Figure 1). All English-language studies completed in humans were reviewed. Studies referencing treatment with high-dose amphotericin, defined as daily receipt of an amphotericin B lipid formulation (lipid complex or liposomal) at doses ≥7.5 mg/kg were included. Studies referencing one-time loading doses, prophylaxis, in vitro or animal studies, or those with leishmaniasis were excluded. References of relevant articles were reviewed and added as appropriate.

Figure 1. Literature search flow diagram.



Results

Case series

Nine patients met the inclusion criteria for the case series (Table 1). Patients received an average of 8.9 ± 1.3 mg/kg of liposomal amphotericin B for a duration of 11.0 ± 10.8 days (range 1–34) predominantly for mould infections, including Mucorales, *Fusarium* species and aspergillosis. The average patient age was 49.4 ± 16.8 years, body weight was 88.0 ± 31.3 kg, and most patients (56%) were cared for in the intensive care unit. The average length of hospital stay was 46.3 ± 46.8 days. The median Charlson Comorbidity Index was 3 ([interquartile range 1–5], range 0–10). Most patients (89%) had previously received amphotericin B at an average dose of 4.66 ± 2.22 mg/kg in the course of the same infection as well as other concurrent antifungals (100%). Three patients (33%) were cured of their infection and 6 (67%) died during (*n*=4) or after (*n*=2) their stay. The main adverse effects were increased serum creatinine (*n*=3), changes in heart rhythm (*n*=3) and decreases in potassium levels (*n*=1).

Review of the literature

A total of 959 articles were identified through the PubMed search and review of references. After limiting articles to humans and English language, 637 articles were screened to determine eligibility for inclusion

Table 1. Clinical efficacy and safety of high-dose amphotericin B.

Case	Indication	Amphotericin dose (mg/kg)	Days of treatment (days)	Concomitant antifungal?	Outcomes	Adverse effects
1	Empirical	10	4	Posaconazole	Death during stay	↑ SCr (baseline 0.6 to 1.52 mg/dL)
2	Empirical	7.5	12	Voriconazole	Death after discharge	None reported
3	*Mucor*	10.2	22	Posaconazole; caspofungin	Cure	None reported
4	Empirical	7.5	12	Fluconazole; micafungin	Death during stay	None reported
5	*Cryptococcus*	7.5	3	Flucytosine	Cure	None reported
6	*Candida albicans* and *Mucor*	10	4	Voriconazole; micafungin	Death during stay	↑ SCr (baseline 2.64 to 3.72 mg/dL); change in heart rhythm
7	Invasive fungal sinusitis plus disseminated fungal infection	10	34	Posaconazole	Cure	↑ SCr (baseline 0.69 to 2.12 mg/dL); decrease in K^+ levels (baseline 3.7 to 2.6 mEq/L)[a]; change in heart rhythm
8	*Cryptococcus*	7.53	1	Fluconazole	Death after discharge	None reported
9	*Aspergillus* and *Mucor*	10	7	Fluconazole; voriconazole; micafungin	Death during stay	Change in heart rhythm

[a]Received supplemental K^+.
SCr, serum creatinine.

based on pre-determined criteria. A total of 11 manuscripts met inclusion criteria and were included in this review (Table 2).[14–24] Of these, seven were case reports or case series, one was a retrospective evaluation, and three were prospective studies (1 pilot, one open label, one randomized controlled trial). A total of 260 patients, ranging from 8 to 69 years of age, were represented in the published literature. Most patients had an underlying haematological malignancy, and many had previously received lower doses of amphotericin B or alternative antifungal therapies. Favourable response with high-dose therapy across all published literature ranged from 8% to 100%. In multi-patient reports, rates of nephrotoxicity, hepatotoxicity and hypokalaemia were higher in the high-dose groups.

Discussion

In the management of difficult-to-treat invasive mould or dimorphic fungal infections, high doses of liposomal amphotericin B were fairly well tolerated (did not require discontinuation or dose change) in published literature and in nine patients at our institution. Adverse effects predominantly included increases in serum creatinine throughout the course of therapy. If choosing to employ high-dose therapy, clinicians should follow best practices to monitor kidney function and changes in electrolytes daily whilst on amphotericin B therapy. Although response and mortality rates in our case series were consistent with previously reported literature,[14–24] the range of favourable responses in multi-patient studies (8–68%) is still dismally low.

Although high-dose liposomal amphotericin B was tolerated, studies suggest that there may be favourable alternatives or required concomitant therapies for difficult-to-treat infections. First, five reports included surgical resection of the affected location as a concomitant treatment, which has long been known to be the definitive therapy for Mucorales.[14,17,19,21,23,25] Of these, four cases reported successful treatment in five patients, but this high response rate is likely due to publication bias.[14,17,21,23] In the one multi-patient study, 71% of patients received

Table 2. Literature reports of high-dose amphotericin B.

Citation	Patient(s)	Indication	Amphotericin formulation	Amphotericin dose (mg/kg)	Duration of treatment (days)	Concomitant/continued therapy	Outcomes
Barron et al., 2005 (ref.[14])	24-year-old male post BMT	Craniofacial *Rhizopus* spp.	Liposomal	10	14	Daily surgical debridement and AmB nasal washes; dose reduced to 5 mg/kg on day 14 and continued for 79 days	No evidence of infection at 3-month follow-up; no recurrence at 3 years
Cornely et al., 2007 (ref.[15])	94 patients with haematological malignancies	Proven or probable mould infection (97% *Aspergillus*)	Liposomal	10	14	Reduced to 3 mg/kg/day for remainder of therapy	Favourable response in 46% (*versus* 50% in comparator 3 mg/kg/day group); survival at 12 weeks 59% (*versus* 72% in comparator); significantly higher nephrotoxicity and hypokalaemia than comparator
Cudillo et al., 2006 (ref.[16])	34-year-old male with ALL	Skin and sputum *Fusarium* spp.	Liposomal	9	15	Dose escalated from 3 to 5 to 9 mg/kg, then reduced after improvement and continued for 80 days in total	No *Fusarium* recurrence at 6 months; patient died from progressive ALL 1 year later
Jain et al., 2003 (ref.[17])	8-year-old female with ALL	Maxillary sinuses with *Mucormycosis*, *Aspergillus* and *Candida albicans*	Liposomal	25	7	Dose escalated from 5 mg/kg/day after 1 week due to disease progression; changed to itraconazole after completion of HD course; had maxillary sinus debridement	Alive and neurologically stable at 18 months; most recent MRI with complete resolution of brain abscess
Kontoyiannis et al., 2001 (ref.[18])	23-year-old male with Hodgkin's disease	Disseminated aspergillosis	Liposomal	10–15	300	Originally received 7.5 mg/kg/day, then switched to investigational echinocandin plus itraconazole, then switched to 10 mg/kg and escalated from there	Total therapy from initial therapy to discontinuation: 14 months; SCr increased from 0.9 to 2.1 mg/dL; no signs of infection at 7 months post-treatment
Lanternier et al., 2015 (ref.[19])	34 patients, predominantly with haematological malignancies	Mucormycosis	Liposomal	10	28	Surgical therapy concomitantly when deemed necessary	71% received surgery; 31–36% with favourable response at EOT[a]; 21% mortality

(*Continued*)

Table 2. (Continued)

Citation	Patient(s)	Indication	Amphotericin formulation	Amphotericin dose (mg/kg)	Duration of treatment (days)	Concomitant/continued therapy	Outcomes
McLintock et al., 2007 (ref.[20])	34 patients with stem cell transplantation or haematological malignancy	Proven or probable invasive fungal infection	Liposomal	10	5	Dose reduced to 3 mg/kg for ≥9 days after initial 5 days	Median 27 days therapy; day-15 response 68% with 88% survival; EOT response 62% with 74% survival
Ota et al., 2017 (ref.[21])	69-year-old female with AML	Mucorales confirmed as *Cunninghamella bertholletiae*	Liposomal	10	150	Voriconazole prophylaxis prior to treatment; initially received 5 mg/kg/day ×12 days; HD given with concomitant micafungin 150 mg/day; had surgical lobectomy for diagnosis and resection; after 5 months with HD, tapered over four additional months	Total course 284 days; SCr increased from 0.6 to 1.2; remission from AML with no recurrence of mucormycosis at 57 months
	35-year-old male with AML post BMT		Liposomal	10	180	Voriconazole prophylaxis prior to treatment; concomitant micafungin 150 mg/day; therapy tapered after completion of HD; had surgical lobectomy for resection	Total course 240 days; SCr increased from 0.5 to 1.3; nodules cleared prior to therapy discontinuation
Raad et al., 2008 (ref.[22])	90 patients with haematological malignancies *versus* 53 patients receiving posaconazole monotherapy	Salvage therapy for invasive aspergillosis	Liposomal	≥7.5	≥7 (salvage therapy)	52 AmB monotherapy; 38 combined with caspofungin	Response to salvage therapy: 8% *versus* 11% *versus* 40% for HD monotherapy, combination with caspofungin and posaconazole monotherapy, respectively; death within 12 weeks: 65% *versus* 74% *versus* 43%; significantly higher nephrotoxicity and hepatotoxicity in HD groups

(*Continued*)

Table 2. (Continued)

Citation	Patient(s)	Indication	Amphotericin formulation	Amphotericin dose (mg/kg)	Duration of treatment (days)	Concomitant/continued therapy	Outcomes
Revankar et al., 2007 (ref.[23])	46-year-old male with diabetes	Disseminated/ cerebral zygomycosis	Liposomal	10	35	Initially received conventional AmB 1 mg/kg, then AmB lipid complex 5 mg/kg + aerosolized AmB, then transitioned to HD on day 87; sinus resection and craniotomy	Total course 189 days; improvement in inoperable brain lesion seen after 35 days of HD; free of disease at 1 year post therapy
Servais et al., 2019 (ref.[24])	29-year-old male	Pulmonary blastomycosis	Liposomal	7.5	6	Escalated from 5 to 7.5 mg/kg after 9 days	Total 53 days of therapy before transitioning to itraconazole; clinically stable at 12 months after AmB EOT

[a]According to the Segal and Herbrecht criteria, respectively.

ALL, acute lymphocytic leukaemia; AmB, amphotericin B; AML, acute myeloid leukaemia; BMT, bone marrow transplantation; EOT, end of treatment; HD, high dose; SCr, serum creatinine.

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concomitant surgical therapy and overall mortality was 21%.[19] Five reports described combination therapy with azoles, echinocandins or topical therapies (e.g. amphotericin irrigations) with varying success rates.[17,18,21,22,23] Beyond these, two of the included studies evaluated high-dose lipid formulation amphotericin *versus* comparators.[15,22] Raad et al. retrospectively compared posaconazole salvage therapy for invasive aspergillosis to high-dose amphotericin monotherapy or combination with caspofungin.[22] The group receiving posaconazole had markedly higher favourable response rates (complete resolution of clinical, radiographic and microbiology abnormalities, or significant improvement in response to therapy) and lower mortality. In the AmBiLoad trial, there was no difference in favourable overall response (complete or partial resolution of clinical, radiological and microbiological findings) in patients receiving a 14-day load of 3 *versus* 10 mg/kg/day (50% *versus* 46%, respectively), and patients in the 10 mg/kg/day group experienced more nephrotoxicity (defined as an increase in serum creatinine to double baseline value; 14% *versus* 31%, respectively).[15] Of note, these studies were published in 2008 and 2007, respectively (Raad and colleagues et al.[22] included patients presenting from 1994 to 2005), and clinical diagnosis and management of invasive fungal infections has changed substantially since then.

Conclusion

Given the small number of included patients in the published literature, the lack of direct comparators, underwhelming performance of high-dose liposomal amphotericin B in studies with direct comparators, and the incidence of adverse effects with higher doses and longer courses, it is unsurprising that clinical uptake in the use of high-dose liposomal amphotericin B has been slow. Despite this, we are seeing increasing use of higher doses at our institution in the last couple of years. We suspect that this is due to comorbidities or concomitant therapies that make alternative options (azoles, echinocandins, combination therapy) less desirable (drug–drug interactions, prolonged QT intervals, drug intolerance or resistance). As a result, high-dose liposomal amphotericin B alone or in combination with other antifungal agents may be a feasible management strategy for invasive fungal infections with limited treatment options.

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