META-ANALYSIS

Safety and Effectiveness of High-dose Liposomal Amphotericin B: A Systematic Review and Meta-analysis

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ABSTRACT

Background • Although the level of medical care has been improved in recent years, the probability of patients contracting pathogens has increased greatly, with a rising incidence of invasive fungal infections. Deep-seated fungi have become common pathogens of nosocomial infections.

Objective • This study aims to systematically assess the effectiveness, mortality, survival rate, and adverse reactions (ARs) of high-dose (HD) liposomal amphotericin B (L-AMB) for human diseases.

Methods • Ten articles (1661 patients) of randomized controlled trials (RCTs; whether randomized, single-blind, or double-blind) from January 1, 1960, to December 31, 2020, of HD-L-AMB treatment of diseases were retrieved from the PubMed, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials databases. The primary outcome measure was the overall therapeutic effect, and the secondary outcome measures were mortality, ≥10-week survival, and ARs. Data were meta-analyzed using RevMan 5.3.

Results • Ten RCTs involving 1661 patients were included. HD-L-AMB did not show a significant therapeutic advantage in anti-infection treatment. In addition, HD-L-AMB treatment of invasive *Aspergillus* infection led to high mortality and low survival (≥10 weeks, OR = 0.57, 95%CI 0.34–0.94, $P = .03$). According to subgroup analysis, the incidence of ARs and the incidence of renal dysfunction associated with invasive fungal infection treatment were higher with HD-L-AMB than with regular-dose L-AMB.

Conclusion • HD-L-AMB had no obvious advantage for the treatment of diseases and was accompanied by increased mortality, reduced long-term survival, and increased ARs (including renal insufficiency). Therefore, the use of HD-L-AMB to control infections is recommended with caution only when the preferred treatment is contraindicated. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Despite the constant advances in the level of medical treatment, the likelihood of pathogen infection continues to increase. Moreover, the prevalence of invasive fungal infections has increased with the wide application of broad-spectrum antibiotics, immunosuppressants, and cytotoxic drugs, as well as the increasing incidence of organ transplantations, hematologic diseases, malignant tumors, and immune-deficiency diseases. Deep-seated mycoses have become a common pathogen of nosocomial infections, with the common opportunistic and pathogenic fungi being *Candida*, *Histoplasma capsulatum*, and *Aspergillus*.[1] Amphotericin B (AMB), a polyene antifungal drug that acts on fungal cell membrane ergosterol, causes changes in membrane permeability, inducing the leakage of intracellular potassium ions, nucleotides, amino acids, and other substances, and ultimately leading to fungal cell death. AMB has the advantages of stable efficacy, minimal fungal resistance, and a broad antimicrobial spectrum.[2] Clinically, L-AMB is a broad-spectrum antifungal agent used to treat invasive fungi, fungal infections, cryptococcal meningitis, and other diseases in patients intolerant to empirical drugs or azoles.[3] Leishmaniasis is a common skin parasitic infection worldwide which is generally treated with intravenous L-AMB, the only medicine approved by the U.S. Food and Drug Administration for the disease.[4] AMB is commonly used for most invasive fungal infections, including serious endemic fungal infections, such as histoplasmosis, penicilliosis, para-coccidioidomycosis, coccidioidomycosis, blastomycosis, and sporotrichosis.[5-6] However, AMB causes

many adverse reactions (ARs), renal impairment in particular, which limits its clinical use. The AMB dosage form has been modified to reduce ARs. Liposomal amphotericin B (L-AMB) is associated with a lower AR rate and better patient survival compared with traditional AMB dosage forms.[7] This improvement can be explained by the presence of a complex double-layer membrane in L-AMB that is absent in traditional AMB, which encapsulates drugs that can be hydrolyzed by tissue lyase, allowing entry into the infection site and helping to concentrate the drug at the fungal infection site.[8-9] Therefore, L-AMB has become an alternative for patients who cannot tolerate AMB.[10]

Indeed, L-AMB has many clinical advantages. However, due to the shortage of medical funding, many countries cannot use expensive liposomes in large quantities.[11] According to relevant guidelines, the L-AMB dose is recommended to be 3–5 mg/kg/d for invasive fungi, fungal infections, and cryptococcal meningitis, and 3 mg/kg/d for leishmaniasis.[4-6,12] However, as described by the existing research, L-AMB is a new dosage form of AMB encapsulated by bimolecular liposomes with special pharmacokinetic properties, which accumulates in vivo after a high-dosage administration, allowing for a rapid onset of action and making it possible to reach the therapeutic concentration at the next administration.[8] Considering this property, some scholars believe that L-AMB can be administered in high doses to achieve rapid onset of action and reduce administration frequency.[8] To treat invasive fungal infection, L-AmB is injected daily (dose 3-5 mg/kg/day). This is not practical for outpatients requiring antifungal prophylaxis. However, when administered at higher doses (7.5-15 mg/kg), therapeutic levels of L-AmB in tissues can be maintained for more than a week without increased toxicity. Thus, intermittent high-dose administration is supported.[13-14] At present, this scheme has shown significant efficacy and cost-effectiveness in the treatment of many diseases.[15-16] Moreover, given the above characteristics of L-AMB, controlled experiments of HD-L-AMB treatment have been performed to determine whether it can shorten the drug administration time and improve the treatment effect compared with other therapeutic schemes.[17]

Considering the above, the present study included randomized controlled trials (RCTs) to systematically review and meta-analyze HD-L-AMB treatment of human diseases. Our study further evaluated the safety and efficacy of this therapeutic approach to determine if it offers a therapeutic advantage.

METHODS

Protocol and registration

This systematic review and meta-analysis, prepared with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards[18] that have been reported in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022368973).

Literature retrieval

Literature retrieval of RCTs of HD-L-AMB treatment for human diseases from the PubMed, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases was performed electronically and manually. The date range of the published literature electronically retrieved was from January 1, 1960, to December 31, 2020, and manual retrieval was performed to study relevant references in the retrieved literature. The search term used was "high-dose liposomal amphotericin B."

Eligibility and exclusion criteria

The following eligibility criteria were used: 1. RCTs (whether randomized, single-blind, or double-blind) of HD-L-AMB (>5 mg/kg/d) treatment of diseases; 2. Articles with an intravenously administered HD-L-AMB treatment group, allowing for an unlimited treatment course, and a control group receiving regular-dose L-AMB or other drugs.; 3. Articles with study subjects who used L-AMB to treat or prevent infectious diseases, regardless of age and sex; and; 4. Articles with the primary outcome measure including the overall therapeutic effect, and the secondary outcome measures including mortality, ≥10-week survival rate, and ARs.

The exclusion criteria were RCTs that were repeatedly reported or did not include the aforementioned outcome measures or applied other outcome measures; reviews, case reports, and experience summaries; retrospective analyses; and other studies with confusing reports or missing conclusions.

Literature deletion and data acquisition

Two evaluators conducted independent literature screening and data acquisition and then exchanged their evaluations to check. If they disagreed on literature inclusion and data extraction, the opinion of a third evaluator was sought for decision-making. The extracted data mainly included the general characteristics of the eligible articles, which included the author(s), publication year, country, sample size, dose and drug in the HD-L-AMB group (experimental group), dose and drug in the control group, disease type, included population, experiment type, and outcome measures. The studies included were finally confirmed by our authors.

Quality evaluation

We assessed the methodological quality of the included literature by referring to the Cochrane risk of bias tool (Version 5.3).[19] The following specific evaluation contents were included: 1) whether the randomization allocation sequence was generated correctly; 2) whether allocation concealment was performed effectively; 3) whether the blinding was complete confirming double-blinded trials; 4) whether the results data were complete; 5) whether the research reported the results selectively, and; 6) whether other risks were causing a high risk of bias.

Statistical methods

Statistical analysis was performed using Revman version 5.3 software provided by the Cochrane Collaboration. The

summary odds ratio (OR) and the weighted mean difference with 95% confidence intervals (CI) were used for dichotomous and continuous variables, respectively. A chi-square test was applied to determine if the test results were significant. If the heterogeneity test did not reveal statistical significance between studies ($P > .05$, $I^2 < 50\%$), a fixed-effect model (FEM) was used to pool the therapeutic effects data; a random-effects model (REM) was established for calculating the pooled data when the heterogeneity test generated a statistically significant difference ($P \leq .05$, $I^2 \geq 50\%$), and a cautious explanation of the results was applied. Descriptive analyses were performed when the data could not be pooled for other reasons. For publication bias analysis, a funnel plot was drawn to observe the distribution and determine the presence or absence of any potential publication bias.

RESULTS

The PROSPERO registration number for this review is CRD42022368973 (URL: https://www.crd.york.ac.uk/PROSPERO/#myprospero). A total of 741 articles were retrieved through keyword and reference retrieval. Finally, fourteen articles were selected for full-text reading. Two articles were excluded due to ineligibility for the target population, and two articles were excluded due to the retrospective analysis research design. Eventually, ten articles (1,661 patients) were included in this systematic evaluation (Figure 1). All literature was published from 2001 to 2019 in the United Arab Emirates (n = 1), France (n = 3), the United States (n = 2), Europe and Australia (n = 1), Tanzania and Botswana (n = 1), and India (n = 3). The types of diseases included invasive *Aspergillus* infection (n = 4), leishmaniasis (n = 3), acquired immunodeficiency syndrome (AIDS)-related cryptococcal meningitis (n = 2), sepsis (n = 1), and neutropenic fever (n = 1). HD-L-AMB was administered at 10–15 mg/kg/d which was given once, twice, or even three times, and continuously administered at 6–10 mg/kg/d. The drugs used in the control group included regular-dose L-AMB (n = 5), AMB deoxycholate (n = 3), AMB lipid solution (n = 1), posaconazole (n = 1), and no drugs (n = 1). The major features of the studies included are presented in Table 1.

Figure 1. PRISMA flowchart of the study selection process

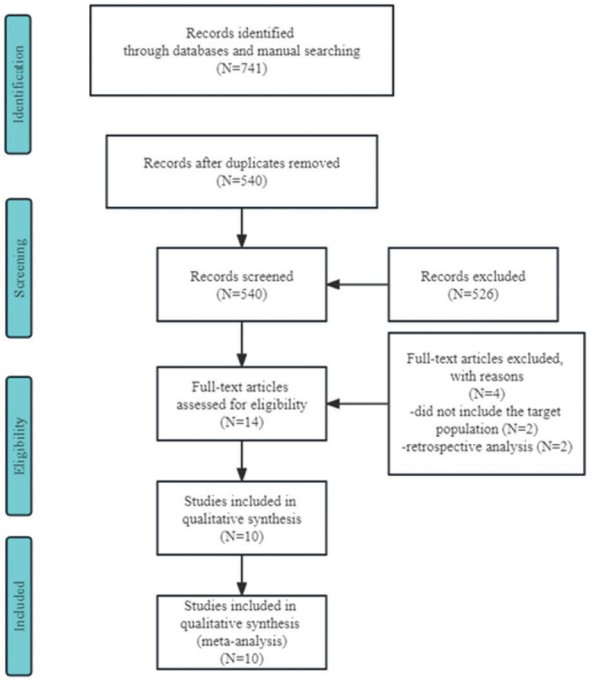


Table 1. Major features of the studies included

Author	Year	Country	Disease	Dose and number of experimental groups	Dose and number of control groups	Experimental design	Primary indicator	Secondary indicator
Caillot et al.[20]	2007	France	invasive fungal infections	L-AMB 10.0 mg/kg/day ≥14 days (n = 15)	L-AMB 3 mg/kg/day+ caspofungin at least 14 days (n = 15)	a national, multicenter, pilot, prospective, randomized open trial	favorable response	time to favorable overall response, time to complete response, survival at the end of treatment (EOT), percentage of patients with recurrent infections, and survival during the 4-week post-treatment follow-up
Hamill et al.[21]	2010	United States and Canada	acquired immunodeficiency syndrome (AIDS) and acute cryptococcal meningitis	L-AMB 6 mg/kg/day 11–21 days (n = 94)	AMB 0.7 mg/kg/day (n = 87) or L-AMB 3 mg/kg/day (n = 86)11–21 days	a national, multicenter, randomized, double-blinded trial	incidence of mycological success at week 2	(1) therapeutic success at week 10 among the mycological evaluable patients who completed study treatment or died during weeks 2–10; (2) survival at week 10
Sundar et al.[22]	2010	India	Visceral leishmaniasis	L-AMB 10 mg/kg single dose (n = 304)	(after a 5-mg test dose), AMB 1 mg/kg/day 15 alternate days (n = 108)	A multicenter, open-label, noninferiority, randomized controlled trial	therapeutic effect	adverse events
Cornely et al.[23]	2007	Europe and Australia	invasive fungal infections	L-AMB 10 mg/kg/day 14 days (n = 94)	L-AMB 3 mg/kg/day 14 days (n = 107)	double-blind trial	compare overall response	survival of up to 12 weeks and the safety profiles
Ellis et al.[24]	2009	UAE	neutropenic fever	L-AMB 10 mg/kg on day 1, 5 mg/kg on days 3 and 6 (n = 15)	L-AMB 3 mg/kg/day 14 days (n = 15)	open, randomized clinical trial	safety parameters	feasibility of using L-AMB, good efficacy for the composite, emergence of invasive fungal infections (IFI), and defervescence
Azoulay et al.[25]	2017	France	critically ill septic	L-AMB 10 mg/kg/week for 14 days (n = 21)	No drug (n = 69)	pilot, multicenter, open-label, prospective study	evaluation of the safety and tolerance	evaluation of the morbidity parameters (length of stay in the ICU and hospital) and assessment of the IFI incidence
Raad et al.[26]	2008	United States	invasive fungal infections	L-AMB ≥7.5 mg/kg/day (n = 52)	orally or via 800 mg Posaconazole (n = 53)	compassionate-use trials	therapy response	toxicity and duration of therapy
Jarvis et al.[27]	2019	Botswana and Tanzania	AIDS and acute cryptococcal meningitis	(1) L-AMB 10 mg/kg on day 1 (n = 18); (2) L-AMB 10 mg/kg on day 1 and 5 mg/kg on day 3 (n = 20); (3) L-AMB 10 mg/kg on day 1 and 5 mg/kg on days 3 and 7 (n = 20)	L-AMB 3 mg/kg/day for 14 days (n = 21)	open-label phase 2 randomized noninferiority trial	the mean rate of decrease in cerebrospinal fluid (CSF) cryptococcal	mortality at 2 and 10 weeks; proportions of patients in each treatment arm with clinical and laboratory-defined-grade 3/4 adverse events
Thakur et al.[28]	2001	India	Visceral leishmaniasis	L-AMB 15 mg/kg single dose (n = 17)	AMB 1 mg/kg for 20 days (n = 17)	pilot study	favorable response	adverse events
Sundar et al.[29]	2014	India	Visceral leishmaniasis	L-AMB 15 mg/kg single dose (n = 124)	ABLE 15 mg/kg/single dose (n = 376)	prospective, multicentric, randomized, open-label, comparative Phase III study	clinical improvement	adverse events

Figure 2. Risk of bias assessment of the selected studies shows the quality evaluation and bias risk assessment of the literature included. Of the 10 included articles, 4 were high-quality RCTs that detailed the blinding and allocation. Another four articles were open-label RCTs, and the remaining two articles were observational controlled trials with a risk of bias since there was no blinding in the allocation.

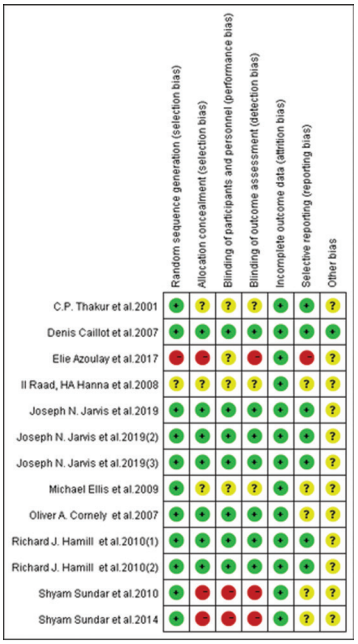
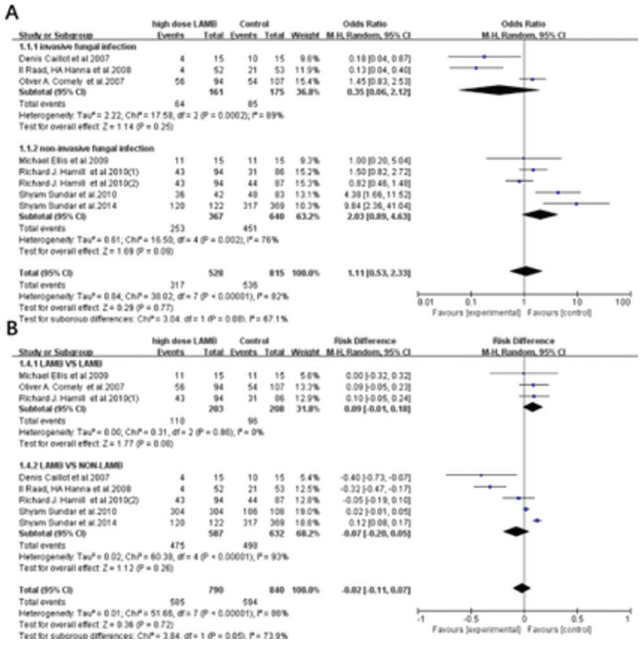


Figure 3. Forest plots for different subgroup analyses to the response of high-dose L-AMB. (A) Invasive fungal infection vs. noninvasive fungal infection; (B) High-dose L-AMB vs. regular-dose and high-dose L-AMB vs. others. Horizontal lines represent the confidence intervals of the findings; squares, where the location represents the effect size, and the size indicates the weight, contributing to the meta; and diamonds, represent the merged results.



Effect of HD-L-AMB on therapeutic efficacy

Six articles described the overall response rate (ORR) of patients, three of which were high-quality RCTs. Of the six articles, there were 3 articles on anti-invasive treatment for *Aspergillus* infection and 3 on anti-noninvasive *Aspergillus* infection treatment. Analysis was performed using a REM given the significant heterogeneity among articles (P < .00001, I^2 = 82%). No significant inter-group difference was identified in the ORR (OR = 1.11, 95%CI 0.53–2.33, P = .77). The significant heterogeneity among studies was persistent in the subgroup analysis of anti-invasive *Aspergillus* infection treatment (P = .0002, I^2 = 89%), and statistical significance was absent in the ORR between groups (OR = 0.35, 95%CI 0.06–2.12, P = 0.25). In addition, significant heterogeneity was detected between studies on anti-noninvasive *Aspergillus* infection treatment (P = .002, I^2 = 76%); but still, no evident inter-group difference in the ORR was identified (OR = 2.03, 95%CI 0.89–4.63, P = .09) (Figure 3A).

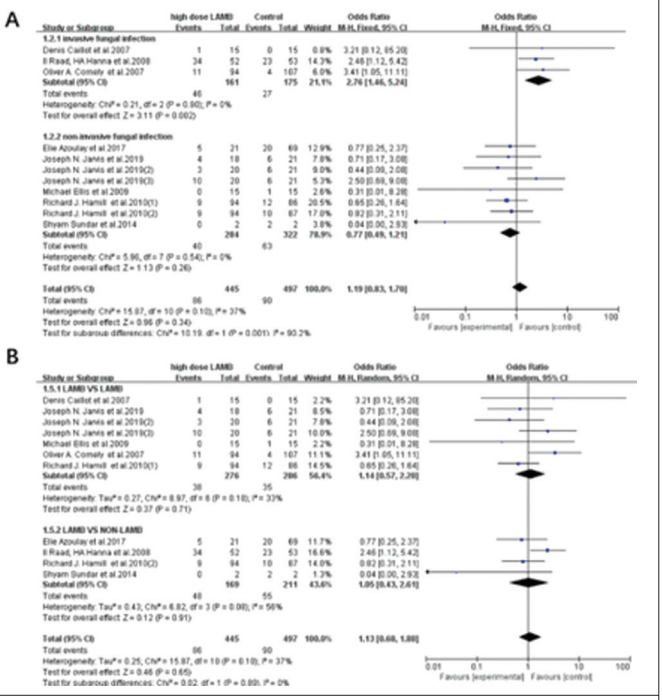
Furthermore, subgroup analyses were performed to compare HD-L-AMB with regular-dose L-AMB and other non-L-AMB drugs. Eight articles were included in total, three of which were high-quality RCTs. Three articles compared HD-L-AMB with regular- or low-dose L-AMB, and five articles compared HD-L-AMB with non-L-AMB drugs. No heterogeneity was found in studies that compared high- and low-dose L-AMB groups (P = .86, I^2 = 0); hence, a FEM was used for subsequent analysis. The results revealed no statistical significance in the ORR between groups (OR = 0.09, 95%CI −0.01 to 0.18, P = .07). Obvious heterogeneity was found between studies in the comparison of treatment with non-L-AMB drugs (P < .00001, I^2 = 93%), suggesting the use of a REM for analysis. The two groups also showed no significant difference in the ORR (OR = −0.07, 95%CI −0.20 to 0.05, P = .26) (Figure 3B).

Effects of HD-L-AMB on mortality

Eight articles reported patient mortality, four of which were high-quality RCTs. Of these eight articles, three were about anti-invasive *Aspergillus* infection treatment, and five were about anti-noninvasive *Aspergillus* infection treatment. The REM was adopted since no obvious heterogeneity was identified between studies (P = .10, I^2 = 37%). The two groups showed no statistical significance in mortality (OR = 1.19, 95%CI 0.83–1.70, P = .34). In the subgroup analysis, no heterogeneity was found among studies on anti-invasive *Aspergillus* infection treatment (P = .90, I^2 = 0), indicating the use of the FEM for analysis. The analysis revealed the presence of statistical significance in mortality between groups, with patients receiving HD-L-AMB at a higher risk of mortality (OR = 2.76, 95%CI 1.46–5.24, P = .002, involving two high-quality RCTs with high-level evidence). The FEM was also applied to the analysis of studies on anti-noninvasive *Aspergillus* infection treatment that were not heterogeneous (P = 054, I^2 = 0%), and the two groups were found to have no statistical significance in mortality as well (OR = 0.77, 95%CI 0.49–1.21, P = .26) (Figure 4A).

Furthermore, subgroup analyses were carried out to compare HD-L-AMB, regular-dose L-AMB, and other non-L-AMB drugs. Nine articles were included, including four high-quality RCTs. Of the nine articles, three compared HD-L-AMB with regular- or low-dose L-AMB, and five compared HD-L-AMB with non-L-AMB drugs. Given the absence of significant heterogeneity among studies in the comparison of high- and low-dose L-AMB by subgroup analysis (P = .18, I^2 = 33%), a FEM was adopted for analysis, which revealed no statistical significance in mortality between the groups (OR = 1.15, 95%CI 0.70–1.90, P = .57). Additionally, significant heterogeneity was identified between studies in the comparison of treatment with non-L-AMB drugs (P = .08, I^2 = 56%), and the REM was therefore selected. The two groups were found to have a significant difference in mortality (OR = 1.05, 95%CI 0.43–2.61, P = .91) (Figure 4B).

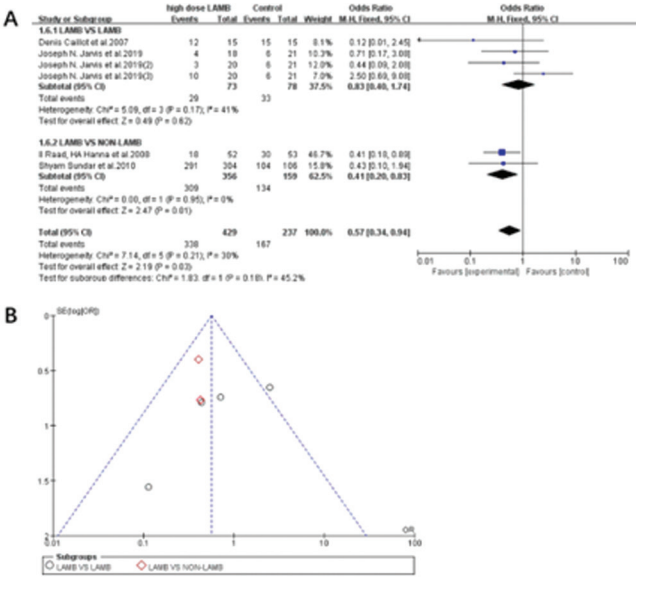
Figure 4. Forest plots for different subgroup analyses of mortality after high-dose L-AMB. (A) Invasive fungal infection vs. noninvasive fungal infection; (B) High-dose L-AMB vs. regular-dose or high-dose L-AMB vs. others. Horizontal lines represent the confidence intervals of the findings; squares, where the location represents the effect sizes, and the size represents the weight, contributing to the meta; diamonds, representing the merged results.



Effect of HD-L-AMB on the ≥10-week survival rate

Four articles reported ≥10-week survival rates in patients receiving treatment, including two high-quality RCTs. Among them, two articles compared HD-L-AMB with regular- or low-dose L-AMB, and the other two compared HD-L-AMB with non-L-AMB drugs. The FEM was used for analysis given the absence of obvious heterogeneity between studies (P = .21, I^2 = 30%). HD-L-AMB was found to reduce the ≥10-week survival rate in patients receiving treatment compared with the control group (OR = 0.57, 95%CI 0.34–0.94, P = .03, involving two high-quality RCTs with a high level of evidence) (Figure 5).

Figure 5. Different subgroup analyses of the ≥10-week survival of high-dose L-AMB vs. regular-dose and high-dose L-AMB vs. others. (A) Forest plot; (B) Funnel plot. Horizontal lines represent the confidence intervals of the findings; squares, where the location represents the effect size, and the size represents the weight, contributing to the meta; diamonds, representing the merged results.

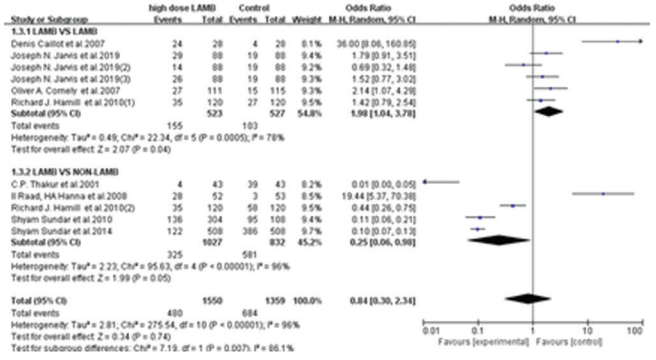


Effect of HD-L-AMB on overall ARs

Eight articles reported on the ARs of patients, four of which were high-quality RCTs. Of the eight articles, two compared HD-L-AMB with regular- or low-dose L-AMB, and two compared HD-L-AMB with non-L-AMB drugs. The FEM was applied for analysis due to the presence of obvious heterogeneity (P < .00001, I^2 = 96%). The two groups showed no significant difference in the incidence of overall ARs (OR = 0.84, 95%CI 0.30–2.34). Further subgroup analysis showed obvious heterogeneity between studies comparing L-AMB treatment (P = .0005, I^2 = 78%), so the REM was adopted for analysis. The results revealed a higher overall AR rate in the HD group (OR = 1.98, 95%CI 1.04–3.78, P = .04, involving four high-quality RCTs with high-level evidence). Significant heterogeneity was also observed in studies comparing non-L-AMB treatment (P < .00001, I^2 = 96%). The overall AR rate was lower in the HD-L-AMB group than in the non-L-AMB group (OR = 0.25, 95%CI 0.06–0.98, P = .05, involving one RCT with a moderate level of evidence) (Figure 6).

Among the various ARs, renal dysfunction was reported in eight articles, hypokalemia in six, infusion reactions in five, hepatic injury in five, anemia in three, and nausea in three. Significant heterogeneity was noticed between studies in renal dysfunction (P = .01, I^2 = 57%), suggesting the use of the REM. No significant inter-group difference was identified

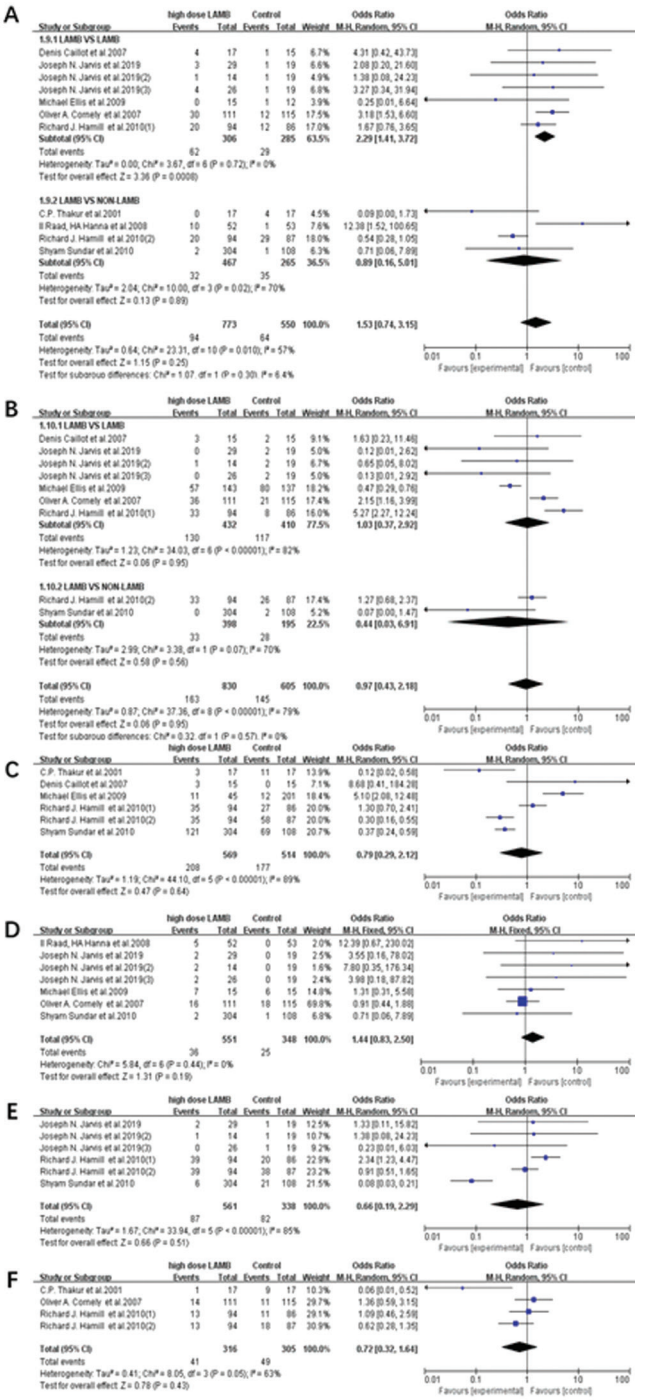
Figure 6. Forest plots for different subgroup analyses of the adverse reactions of high-dose L-AMB vs. regular-dose L-AMB and high-dose L-AMB vs. others. Horizontal lines represent the confidence intervals of the findings; squares, where the location represents the effect size, and the size represents the weight, contributing to the meta; diamonds, representing the merged results.



in the incidence of overall renal dysfunction (OR = 1.53, 95%CI 0.74–3.15, P = .25). Similarly, in the subgroup analysis, no significant heterogeneity was found among studies comparing high- and regular-dose L-AMB treatment (P = .72, I^2 = 0%). The FEM was used because the incidence of overall ARs, manifested as renal dysfunction, was significantly higher in patients receiving HD-L-AMB than in those receiving a regular-dose L-AMB (OR = 2.28, 95%CI 1.42–3.67, P = .0006, including four RCTs with a high level of evidence). We also found significant heterogeneity among studies comparing HD-L-AMB with non-L-AMB treatment (P = .02, I^2 = 70%) and no significant difference in the overall renal dysfunction between groups (OR = 0.89, 95%CI 0.16–5.01, P = .89) (Figure 7A).

The REM was also used given the presence of significant heterogeneity among studies on hypokalemia (P < .00001, I^2 = 79%). The two groups were not statistically different in the overall incidence of hypokalemia (OR = 0.97, 95%CI 0.43–2.18, P = .95) (Figure 7B). Obvious heterogeneity was also observed among studies in the incidence of infusion reactions (P < .00001, I^2 = 89%), suggesting the use of the REM as well. The incidence of infusion reactions was not statistically different between groups (OR = 0.79, 95%CI 0.29–2.12, P = .64) (Figure 7C). Furthermore, the FEM was selected since there was no significant heterogeneity among studies in the incidence of hepatic injury (P = .44, I^2 = 0%), which identified no statistical inter-group difference (OR = 1.44, 95%CI 0.83–2.50, P = .19) (Figure 7D). Moreover, the REM was used for analysis due to the absence of obvious heterogeneity among the studies on anemia (P < .00001, I^2 = 85%), which revealed no statistical inter-group difference in the overall incidence of anemia (OR = 0.66, 95%CI 0.19–2.29, P = .51) (Figure 7E). In addition, there was significant heterogeneity among studies on nausea (P = .05, I^2 = 63%). The analysis using the REM showed no significant difference in the overall nausea rate between groups (OR = 0.72, 95%CI 0.32–1.64, P = .43) (Figure 7F).

Figure 7. Forest plots for different subgroup analyses of the different types of adverse reactions of high-dose L-AMB. (A) Creatinine elevation; (B) Hypokalemia; (C) Infusion reactions; (D) Hepatic injury; (E) Anemia; (F) Nausea. Horizontal lines represent the confidence intervals of the findings; squares, where the location represents the effect size, and the size represents the weight, contributing to the meta; diamonds, representing the merged results.



DISCUSSION

At present, the maintenance regimen of 10 mg/kg/d for invasive *Aspergillus* treatment and the single administration regimen of 15 mg/kg for anti-leishmaniasis treatment are frequently reported as HD-L-AMB administration regimens.[17] Currently, the therapeutic scheme of HD-L-AMB is supported by multiple published animal experiments, clinical experience, case reports, and research. For example, a previous animal experiment showed that 10 mg/kg L-AMB extended the maintenance time of blood drug concentration in L-AMB therapy. When treating granulocytopenia-induced fever, an intermittent therapeutic regimen of 10 mg/kg L-AMB for the first dose and then 5 mg/kg given on the 1st, 3rd, and 6th days of treatment achieved a better effect than continuous L-AMB therapy (3 mg/kg).[16] The results of clinical case reports and non-control studies also suggest that single or multiple HD-L-AMB administrations can achieve good clinical efficacy for the prevention and management of fungal infection in transplant patients or other immunosuppressive patients, with good tolerance as well.[30-32] In addition, single-dose L-AMB (10–20 mg/kg/d) is reported to contribute to better efficacy and lower toxicity in the treatment of leishmaniasis.[33]

This study systematically analyzed the efficacy, mortality, ≥10-week survival, and ARs of different drugs and HD-L-AMB in the treatment of different diseases. Both overall and subgroup analyses showed that the effect of HD-L-AMB in anti-infection treatment was equivalent to that of other treatment schemes, whether compared with other drugs or its regular-dose scheme. However, in the treatment of invasive *Aspergillus* infection, HD-L-AMB was associated with higher mortality and lower ≥10-week survival. A descriptive analysis of all the included literature was further performed for heterogeneity assessment. First, efficacy analysis was conducted by selecting the cases with complete or partial remission and excellent or good responses to the therapeutic drugs mentioned in the literature. The results showed that HD-L-AMB did not show a greater advantage in efficacy, with an ORR slightly lower than that of other schemes. Considering the greater heterogeneity, two subgroups were established for subsequent analysis. Specifically, in the treatment of invasive *Aspergillus* infection, the three reference drugs included in the literature were azoles, regular-dose L-AMB, and L-AMB + caspofungin, which were used to treat malignant tumor patients with hematologic diseases. For such patients, all of the therapeutic schemes mentioned above are either the first-line treatment options or alternatives recommended by the guidelines.[34] The HD-L-AMB failed to exhibit a more obvious advantage than these schemes, and even when administered at 7.55–10 mg/kg body weight per day for ≥2 weeks, L-AMB did not improve disease outcomes more significantly.[20,23,26] However, during the literature review, a retrospective study was conducted that confirmed the efficacy of HD-L-AMB for chronic disseminated candidiasis. Chronic disseminated candidiasis, also commonly known as hepatosplenic candidiasis, is a complication of immunosuppressive patients with hematologic disorders, often involving the liver and spleen.[35] The Infectious Diseases Society of America recommended an initial dose of 3–5 mg/kg L-AMB daily for echinocandins. Treatment should continue until radiographic evidence of lesion regression during the follow-up period, which generally takes several months.[6] This retrospective study analyzed the effectiveness and safety of L-AMB in the treatment of chronic-disseminated candidiasis in patients with hematologic diseases. It examined the difference between regular dose (3 mg/kg/d) and HD (5 mg/kg/d) L-AMB. Despite the retrospective nature of the analysis, this study strongly supported the efficacy of HD-L-AMB, given that there was no case of treatment failure and only one case of discontinuation of chemotherapy due to infection. At the same time, there were no cases of treatment success in patients on conventionally dosed L-AMB schemes.[36] Accordingly, HD-L-AMB may have advantages in the treatment of chronic disseminated candidiasis to some extent. However, to date, no RCT has been conducted for this disease. Subsequently, another subgroup analysis compared the efficacy between HD-L-AMB and regular-dose L-AMB or non-L-AMB drugs. However, no obvious differences were identified, and HD-L-AMB showed no significant therapeutic advantages over regular-dose L-AMB. Therefore, from the standpoint of efficacy, HD-L-AMB is recommended when there are contraindications to the use of other preferred regimens for treating granulocyte deficiency-induced fever, AIDS-related cryptococcal meningitis, and leishmaniasis. HD-L-AMB can be considered and may play a better role in treating chronic disseminated candidiasis. Inconsistencies in efficacy evaluation and subjectivity in reviewed articles lead to high heterogeneity in efficacy analysis, according to our authors. Furthermore, in the analysis of mortality and ≥10-week survival, no obvious heterogeneity was identified as the outcome measures were relatively unified, and the forest plot of the ≥10-week survival rate was symmetric with relatively low overall bias. In this analysis, three groups of data were extracted and included from a report describing a 2019 phase II, noninferiority, controlled trial in Tanzania and Botswana. This trial comparatively analyzed the bactericidal activity of three HD-L-AMB administrations (single-dose 10 mg/kg vs. 10 mg/kg on day 1 and 5 mg/kg on day 3 vs. 10 mg/kg on day 1 and 5 mg/kg on days 3 and 7) with regular-dose L-AMB (3 mg/kg/d) for early-stage cryptococcal meningitis. As a result, the three groups exhibited no significant differences in efficacy and mortality. However, considering patients' treatment compliance, the single administration mode was included in a phase III trial for re-validation.[27] Notably, the trial was designed to compare the HD and regular-dose L-AMB schemes, and all data were collected from one high-quality RCT. Therefore, in our study, all three groups of data were systematically analyzed. To exclude potential influences, the overall results were compared after including and excluding eligible articles. The results revealed no significant heterogeneity among the groups, without any change in the final results (results not released). Regarding patient mortality, similar results were reported in a 2021 meta-analysis comparing

mortality after the use of echinocandins and polyenes. The mortality was significantly higher after initial L-AMB therapy than after echinocandins for the treatment of candidemia, which was possibly related to the higher AR of nephrotoxicity caused by L-AMB.[37] Another study also confirmed the significant increase in mortality due to AMB therapy-induced renal failure (54% vs. 16%).[38] Liposomes are usually associated with a lower incidence of nephrotoxicity than ordinary dosage forms, but they contribute to a risk of renal failure during treatment.[39] Similarly, our analysis of mortality and ≥10-week survival rate of the literature also showed that hepatorenal toxicity might be higher in patients with HD-L-AMB than in those with other therapeutic regimens.[23,26] Therefore, the higher mortality and lower ≥10-week survival rate associated with HD-L-AMB may also be closely linked to ARs, especially nephrotoxicity.

Similarly, in the analysis of ARs, the HD-L-AMB group was associated with an elevated incidence of ARs compared with the regular-dose group, which was also commonly reported in the reviewed literature in this study. Subgroup analysis showed a higher incidence of renal insufficiency in the HD-L-AMB group, with no significant difference in other ARs. Several studies have documented that L-AMB induced renal insufficiency in a dose-dependent manner, which was also confirmed in our research.[39] Therefore, the increase in the risk of renal insufficiency will restrict the choice of the HD-L-AMB therapeutic scheme. An increase in nephrotoxicity would increase not only the drug burden but also patient mortality.[38] Although the incidence of ARs was lower for HD-L-AMB than for non-L-AMB drugs, the result was highly heterogeneous, so further subgroup analysis was performed. This subgroup analysis included three articles on L-AMB treatment of leishmaniasis, with two controlled studies showing that a single dose of HD-L-AMB (10 mg/kg or 15 mg/kg) contributed to a lower AR rate and was better tolerated than 1 mg/kg of AMB administered for 15–20 consecutive days.[22,28] However, these trials were all open-label and emphasized the economic advantages of HD-L-AMB for leishmaniasis, so they might have been affected by publication bias. Considering the above, our authors proposed that the incidence of ARs might be lower than other schemes only if a single HD of L-AMB is given to treat leishmaniasis. Hypokalemia is also one of the most common ARs of L-AMB. In the present meta-analysis, the incidence of hypokalemia associated with HD-L-AMB was similar to that associated with regular-dose L-AMB. We speculated that there may be a more complicated mechanism underlying L-AMB-induced hypokalemia than that of renal insufficiency.

This study had some limitations that must be considered. This meta-analysis included four open-label controlled trials and two observational trials, which may have led to some bias in the conclusions. However, given the significant differences in the results, >50% of the high-quality RCTs were involved in these analyses, which to some extent supports the guiding significance of the generated results. In the analysis of the heterogeneity of the conclusions, the inclusion of some articles might explain the high bias of some results. Nevertheless, further exclusion of the data extracted from these trials had no significant effect on the outcome measures and heterogeneity. Moreover, considering the relatively strict operability of these trials, the publication of the final results did not show an obvious allocation difference after discussion within our research group. Hence, these articles were still included in the overall analysis. Furthermore, literature retrieval for this meta-analysis was limited to documents published in English. The reason was that the search by keywords in Chinese databases (CNKI, Wanfang, and VIP) in advance did not retrieve high-quality RCTs but mostly case analyses instead. Therefore, literature retrieval in Chinese databases was not introduced in the Methods section of this study. Another reason was that L-AMB in China is generic, and the data reported in Chinese research might be different from that in other countries. Moreover, the number of literature included and high-quality RCTs analyzed is limited, which may be related to the high price of L-AMB and the difficulty in accessing the drug due to the restrictions on medical insurance coverage in some countries.[40] Additionally, in the current guidelines, HD-L-AMB is not mentioned or recommended for the management of the aforementioned diseases, which also restricts the implementation of relevant clinical trials in various countries. Notably, however, our study considered these limitations and performed several subgroup analyses. The findings eventually obtained in this study should be of some value in guiding clinical practice.

CONCLUSION

In conclusion, our findings suggest that HD-L-AMB has no obvious advantage in treatment, elevating the risk of mortality, reducing long-term survival, and increasing the possibility of developing renal insufficiency. Therefore, it is recommended that HD-L-AMB be carefully restricted for infection control and only used when there are contraindications to the use of other preferred schemes. It is hoped that our findings can provide a useful reference for better clinical application of L-AMB.

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AUTHOR CONTRIBUTIONS

XY Fu drafted the manuscript and the main plan design and finally approved the inclusion of the selected studies from the literature; CP Zhang and XR Lin independently screened and evaluated the literature; XF Zheng and J Yan were the third party to further evaluate the disputed documents; QB Liu evaluated and guided the overall plan and article writing of the study.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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