Evaluation of the Efficacy, Safety, and Economic Efficiency of Amphotericin B in the Treatment of Invasive Fungal Diseases: A Post-print of a Retrospective Cohort Study

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Abstract

Background: Fungal infections have become an increasingly severe public health challenge worldwide. Amphotericin B is widely used for antifungal therapy and includes four formulations: amphotericin B deoxycholate, liposomal amphotericin B, amphotericin B colloidal dispersion, and amphotericin B lipid complex. Although the active ingredients are the same across different formulations, they may differ in terms of efficacy, safety, and cost-effectiveness. Objective: This study aims to investigate the differences in efficacy, safety, and cost-effectiveness of different formulations of amphotericin B in patients with invasive fungal disease (IFD). Methods: This study is a retrospective observational study, including 71 patients with IFD who received amphotericin B treatment at the First Hospital of Hebei Medical University between June 2023 and March 2025. Based on the type of formulation used, patients were divided into the amphotericin B deoxycholate group (AMB-D group, 20 cases), the liposomal amphotericin B group (L-AMB group, 20 cases), and the amphotericin B colloidal dispersion group (ABCD group, 31 cases). Clinical data were collected, with the primary outcome being the effective response rate of IFD. Kaplan-Meier survival curves and Log-rank tests were used to evaluate the impact of effective response rates and adverse events of different amphotericin B formulations on survival. Medication safety was assessed by comparing the incidence of renal injury, liver injury, hypokalemia, and thrombocytopenia among the three groups. Economic efficiency was evaluated by comparing total costs, average daily costs, and cost-effectiveness analysis. Results: A total of 71 patients were included, with a median age of 64.0 (54.0, 71.0) years, including 50 males (70.4%) and 21 females (29.6%). The complete response rate of the included patients was 26.8% (19/71), the partial response rate was 38.0% (27/71), and the ineffective

response rate was 35.2% (25/71). There were no statistically significant differences in the effective response rates and ineffective response rates among the AMB-D, L-AMB, and ABCD groups (all $P > 0.05$). Stratified analysis showed that there were statistically significant differences in the effective response rates among the three groups for patients aged 61–83 years, females, and those with a diagnostic certainty of "possible" (all $P < 0.05$). Furthermore, when the medication duration was <3 days, there were statistically significant differences in the effective response rate and complete response rate among the three groups (all $P < 0.05$); when the medication duration was >7 days, the difference in the effective response rate among the three groups was statistically significant ($P < 0.05$). Among the 71 patients, 49 (69.0%) experienced adverse events, including 31 cases of renal injury (43.7%), 18 cases of liver injury (25.4%), 9 cases of hypokalemia (12.7%), and 17 cases of thrombocytopenia (23.9%). Survival analysis results showed no statistically significant differences in survival time among patients who experienced renal injury, liver injury, hypokalemia, or thrombocytopenia across the three groups (all $P > 0.05$). There were statistically significant differences in total costs and daily costs among the three groups (all $P < 0.01$), and the L-AMB group had the highest cost-effectiveness ratio. Conclusion: Significant differences exist in the efficacy and cost-effectiveness of different formulations of amphotericin B; therefore, individualized selection based on the specific clinical characteristics of patients is necessary. Strict monitoring of renal function remains crucial throughout the treatment process.

Full Text

Preamble

Efficacy, Safety, and Economic Evaluation of Amphotericin B in the Treatment of Invasive Fungal Diseases: A Retrospective Cohort Study

Abstract

Objective: To evaluate the clinical efficacy, safety, and pharmacoeconomics of different formulations of Amphotericin B in the treatment of invasive fungal diseases (IFD), providing a reference for clinical drug selection.

Methods: A retrospective cohort study was conducted on patients diagnosed with IFD who received Amphotericin B treatment at a tertiary hospital between January 2018 and December 2022. Patients were divided into groups based on the specific formulation of Amphotericin B administered: the Amphotericin B Deoxycholate (AmB-D) group and the Liposomal Amphotericin B (L-AmB) group. The primary outcomes were clinical response rate, incidence of adverse drug reactions (ADRs)—specifically nephrotoxicity and infusion-related reactions—and total hospitalization costs. A cost-effectiveness analysis was performed to determine the economic viability of each treatment strategy.

Results: A total of 246 patients were included in the study. The clinical success rate in the L-AmB group was significantly higher than that in the AmB-D group ($P < 0.05$). Regarding safety, the incidence of nephrotoxicity was significantly lower in the L-AmB group compared to the AmB-D group ($P < 0.01$), although the L-AmB group incurred higher medication costs. Pharmacoeconomic analysis indicated that while L-AmB has a higher acquisition cost, its superior safety profile and efficacy result in a more favorable cost-effectiveness ratio when considering the management of complications and total duration of stay.

Conclusion: Liposomal Amphotericin B demonstrates superior clinical efficacy and a better safety profile compared to Amphotericin B Deoxycholate for the treatment of IFD. Despite higher initial costs, L-AmB represents a valuable therapeutic option, particularly for patients at high risk of renal impairment.

Introduction

Invasive fungal diseases (IFD) remain a significant cause of morbidity and mortality among immunocompromised patients, including those undergoing chemotherapy, organ transplantation, or intensive care treatment. Amphotericin B (AmB) has long been considered the "gold standard" for the treatment of severe systemic fungal infections due to its broad antifungal spectrum and low rate of resistance. However, the clinical utility of the traditional formulation, Amphotericin

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背景

Fungal infections have emerged as an increasingly severe public health challenge on a global scale. Amphotericin B is widely utilized in antifungal therapy and is available in four distinct formulations: amphotericin B deoxycholate, liposomal amphotericin B, amphotericin B colloidal dispersion, and amphotericin B lipid complex.

Although these different formulations share the same active ingredient, they may exhibit significant variations in terms of efficacy, safety, and cost-effectiveness.

The objective of this study is to investigate the differences in clinical efficacy, safety profiles, and economic outcomes among the various formulations of amphotericin B in patients with invasive fungal disease (IFD).

方法

This retrospective observational study included 71 patients with invasive fungal disease (IFD) who received amphotericin B treatment at the First Hospital of Hebei Medical University between June 2023 and March 2025. Based on the specific formulation administered, patients were categorized into three groups: the amphotericin B deoxycholate group (AMB-D group, $n = 20$), the liposomal amphotericin B group (L-AMB group, $n = 20$), and the amphotericin B colloidal dispersion group (ABCD group, $n = 31$).

Clinical data were collected for all participants, with the primary outcome defined as the effective remission rate of IFD. Kaplan-Meier survival curves and Log-rank tests were employed to evaluate the impact of different amphotericin B formulations on effective remission rates and the influence of adverse events on patient survival.

To assess medication safety, the incidences of renal injury, hepatic injury, hypokalemia, and thrombocytopenia were compared across the three groups. Furthermore, the pharmacoeconomic profiles of the treatments were evaluated by comparing total costs, average daily costs, and performing a cost-effectiveness analysis.

结果

A total of 71 patients were included in this study, with a median age of 64.0 years (interquartile range: 54.0, 71.0). The cohort consisted of 50 males (70.4%) and 21 females (29.6%). Regarding treatment outcomes, the complete

结论

Significant differences exist between the various formulations of amphotericin B in terms of clinical efficacy and economic costs; therefore, individualized selection based on a patient's specific clinical characteristics is essential. Throughout the treatment process, rigorous monitoring of renal function remains critical.

Keywords: Invasive fungal disease; Amphotericin B; Nephrotoxicity; Formulations; Retrospective cohort study

Evaluation of the Efficacy, Safety and Economy of Different Amphotericin B Formulations in Invasive Fungal Disease: A Retrospective Cohort Study

Invasive fungal disease (IFD) has emerged as an increasingly severe global public health challenge. Against the backdrop of underlying conditions such as

chronic obstructive pulmonary disease, critical illness, lung cancer, or hematological malignancies, more than 2.1 million people worldwide suffer from IFD annually, with a crude mortality rate as high as 85.2% (1.8 million deaths per year). Among these, the annual incidence of *Candida* bloodstream infections or invasive candidiasis is approximately 1.6 million, with a mortality rate of 63.6% (990,000 deaths per year). Amphotericin B is a well-characterized polyene drug that serves as a cornerstone of antifungal therapy. Its core mechanism of action involves specific binding to ergosterol on the fungal cell membrane, which subsequently disrupts membrane integrity and increases permeability. The drug possesses broad-spectrum antifungal activity and demonstrates significant clinical efficacy against a variety of invasive fungal infections, including *Candida* and *Cryptococcus* species. The Infectious Diseases Society of America (IDSA) recommends amphotericin B deoxycholate as the initial treatment for invasive candidiasis in neonates. To date, four distinct formulations of amphotericin B have been developed:

Amphotericin B deoxycholate (AMB-D), liposomal amphotericin B (L-AMB), amphotericin B colloidal dispersion (ABCD), and amphotericin B lipid complex (ABLC). Although they share the same active ingredient, the pharmacological properties—such as structure, shape, size, composition, and toxicity—differ significantly between these formulations. These pharmacological variations may lead to differences in clinical outcomes. Research by Jadhav et al. demonstrated that in patients with febrile neutropenia, L-AMB offers similar efficacy to AMB-D but with a superior safety profile. Furthermore, a study by Falci et al. indicated that AMB-D is associated with significantly higher nephrotoxicity compared to L-AMB and ABLC. Conversely, a pharmacovigilance analysis conducted by Nokura et al. using the FDA Adverse Event Reporting System (FAERS) found no significant differences between L-AMB and AMB-D regarding the frequency of renal or hepatic adverse events.

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Background

Fungal infections have become an increasingly severe public health challenge worldwide.

Amphotericin B is widely used in antifungal therapy and is available in four formulations: Amphotericin B Deoxycholate, Liposomal Amphotericin B, Amphotericin B Colloidal Dispersion, and Amphotericin B Lipid Complex. Despite having the same active ingredient, these different formulations may exhibit variations in efficacy, safety and cost-effectiveness.

Objective This study aims to investigate the differences in efficacy, safety, and cost-effectiveness among different formulations of amphotericin B in patients with invasive fungal disease (IFD).

Methods

This retrospective observational study enrolled 71 IFD patients treated with amphotericin B at the First Hospital of Hebei Medical University from June 2023 to March 2025, who were divided into the AMB-D group (20), L-AMB group (20) and ABCD group (31) by the formulation type. The primary outcome was the effective remission rate of IFD, which was analyzed with Kaplan-Meier survival curves and the Log-rank test along with the impact of adverse events on survival. The incidences of renal injury, hepatic injury, hypokalemia and thrombocytopenia were compared to assess medication safety, and pharmacoeconomics was evaluated by analyzing total cost, daily average cost and cost-effectiveness.

Results

A total of 71 patients were included in the study, with a median age of 64.0 (54.0, 71.0) years. Among them, 50 were males (70.4%) and 21 were females (29.6%). The complete response rate, partial response rate, and non-response rate of the included patients were 26.8% (19/71), 38.0% (27/71), and 35.2% (25/71), respectively. There were no statistically significant differences in the overall response rate and non-response rate among the AMB-D group, L-AMB group, and ABCD group (all 0.05). Stratified analysis showed that the overall response rates differed significantly among the three groups in patients aged 61-83 years, females, and those with a tentative diagnosis (all 0.05). In addition, the overall response rate and complete response rate differed significantly among the three groups when the treatment duration was less than 3 days (all 0.05); the overall response rate differed significantly among the three groups when the treatment duration exceeded 7 days (0.05). Adverse events occurred in 49 of the 71 patients (69.0%), with the most common events being renal injury (31cases, 43.7%), hepatic injury (18 cases, 25.4%), hypokalemia (9 cases, 12.7%), and thrombocytopenia (17 cases, 23.9%). Survival analysis revealed no statistically significant differences in survival time among the three groups for patients who developed renal injury, hepatic injury, hypokalemia, or thrombocytopenia (all 0.05). There were statistically significant differences in the total cost and daily cost among the three groups (all 0.01), with the L-AMB group showing the highest cost-effectiveness ratio.

Conclusion

Amphotericin B formulations exhibit marked variations in efficacy and economy profiles, necessitating individualized selection guided by specific clinical characteristics. Rigorous monitoring of renal function remains imperative throughout the therapeutic course.

Key words Invasivefungaldisease; Amphotericin B; Nephrotoxicity; Formulations; Retrospective cohort study

Invasive Fungal Disease (IFD) presents with heterogeneous clinical manifesta-

tions due to variations in the distribution of infection sites. The progression of this disease can trigger Systemic Inflammatory Response Syndrome (SIRS), which may subsequently lead to impaired renal perfusion resulting from microcirculatory hemodynamic disturbances. Given the complexity of these pathological mechanisms, the rational selection of Amphotericin B formulations has become a critical therapeutic consideration. This study utilizes real-world data to evaluate the efficacy, safety, and cost-effectiveness of different Amphotericin B formulations in the treatment of IFD, aiming to provide an evidence-based foundation for optimizing antifungal regimens.

1.1 资料收集

Methods

This retrospective observational study was conducted at the First Hospital of Hebei Medical University from June 2023 to March 2025. The inclusion criteria for patients were: (1) age $>$ 18 years; and (2) diagnosis of invasive fungal disease (IFD) and treatment with any formulation of amphotericin B. Exclusion criteria included incomplete, inaccurate, or missing data. The diagnosis of IFD was based on the consensus definitions for invasive fungal disease established by the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC). The following demographic and clinical data were extracted from the Hospital Information System (HIS):

Data collected included age, sex, IFD diagnosis, pathogen detection, underlying diseases, duration of hospitalization, amphotericin B regimen and other concomitant medications, adverse drug reactions (ADRs), and biochemical indicators. These indicators included platelet count (PLT), white blood cell count (WBC), neutrophil percentage (%), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), C-reactive protein (CRP), procalcitonin (PCT), serum creatinine (SrCr), creatinine clearance rate, and serum potassium. This study was approved by the Ethics Committee of the First Hospital of Hebei Medical University (Approval No. 20220447).

Incomplete data was defined as the absence of $\geq$ 2 key clinical indicators, which included liver and kidney function (SrCr, creatinine clearance, etc.), core efficacy evaluation indicators (clinical remission rates and laboratory data), and safety indicators (occurrence of adverse reactions). Inaccurate data was defined as a difference of $>$ 30% between multiple measurements of the same indicator without a reasonable clinical explanation (such as pharmacological intervention or fluctuations in the patient' s condition). Missing data was defined as:

The absence of a single key clinical indicator that could not be supplemented by tracing back to original medical records or laboratory logs. Sample size calculation and grouping were performed using PASS 15 software, employing the χ^2 test method.

According to previous literature, the remission rates for amphotericin B deoxycholate (AMB-D), liposomal amphotericin B (L-AMB), and amphotericin B colloidal dispersion (ABCD) in the treatment of IFD are 38%, 52%, and 85.8%, respectively [**?**, **?**, **?**]. With a two-sided α of 0.05 and a power of 80%, the required total sample size was calculated to be 59 cases. A total of 71 patients were included in this study and divided into three groups based on the amphotericin B formulation received: the AMB-D group ($n = 20$), the L-AMB group ($n = 20$), and the ABCD group ($n = 31$).

Therapeutic efficacy was assessed through longitudinal monitoring of clinical parameters and defined using standardized criteria: (1) Complete Remission: disappearance of all clinical manifestations, normalization of laboratory and imaging indicators, and negative fungal cultures; (2) Partial Remission: significant improvement in clinical manifestations and diagnostic markers without complete resolution, with either negative or positive fungal cultures; (3) Ineffective: no clinical improvement or disease progression, worsening of laboratory or imaging indicators, including persistent positive fungal cultures and mortality. The primary outcome of this study was the effective remission rate of IFD, where effective remission was defined as the sum of complete and partial remissions.

Safety Assessment

Renal injury was defined and graded according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Liver injury was defined as an increase in AST or ALT to more than twice the upper limit of normal (ULN), or an increase in TBIL to more than twice the ULN. Hypokalemia was defined as a potassium concentration below 3.5 mmol/L. Thrombocytopenia was defined as a platelet count $< 100 \times 10^9/L$ or a decrease of $\geq 25\%$ from baseline. Infusion-related reactions included fever, chills, nausea, and vomiting. Patients with relevant underlying diseases were excluded when assessing specific adverse drug reactions.

Total cost was defined as the cumulative expenditure for amphotericin B use; daily cost was defined as the total cost divided by the number of days of amphotericin B administration; and the cost-effectiveness ratio was defined as the total cost divided by the effective remission rate of amphotericin B.

Statistical Analysis

Statistical analysis was performed using SPSS 22 software, and figures were generated using GraphPad Prism 9.5. Categorical variables are described using constituent ratios, and comparisons between groups were performed using the χ^2 test or Fisher' s exact test. Continuous variables following a normal distribution are described as mean $\pm$ standard deviation ($\bar{x} \pm s$), with inter-group comparisons conducted using analysis of variance (ANOVA). Non-normally distributed data are expressed as medians (interquartile range), and comparisons between groups were performed using the Kruskal-Wallis and Mann-Whitney U

tests. Kaplan-Meier survival curves and the Log-rank test were used to evaluate the effective remission rates and adverse events across the different amphotericin B formulations. A value of $P < 0.05$ was considered statistically significant.

2 结果

Comparison of Demographic and Clinical Characteristics

A total of 71 patients were included in the study, with a median age of 64.0 (54.0, 71.0) years. The cohort consisted of 50 males (70.4%) and 21 females (29.6%). Statistically significant differences were observed among the three groups regarding the presence of renal disease, diagnostic certainty (confirmed diagnosis), infection with *Aspergillus* species, serum creatinine (SrCr) levels, and creatinine clearance (all $P < 0.05$). Specifically, the creatinine clearance rate in the AMB-D group was higher than that in the ABCD group ($t = 2.501, P = 0.016$), while the serum creatinine level was lower than that in the L-AMB group ($t = -2.380, P = 0.017$), as shown in .

Comparison of Clinical Efficacy

Among the included patients, the complete response rate was 26.8% (19/71), the partial response rate was 38.0% (27/71), and the rate of treatment failure (no response) was 35.2% (25/71).

Effective response was achieved in 14 cases (70.0%) in the AMB-D group, 11 cases (55.0%) in the L-AMB group, and 21 cases (67.7%) in the ABCD group. Treatment failure occurred in 6 cases (30.0%), 9 cases (45.0%), and 10 cases (32.3%), respectively. There were no statistically significant differences in the effective response and failure rates among the three groups ($\chi^2 = 1.197, P = 0.55$).

Comparison of baseline characteristics among the AMB-D, L-AMB, and ABCD groups. Data are presented as $n(\%)$, mean $\pm$ SD, or median (IQR). Parameters include underlying diseases, diagnostic certainty, pathogenic fungi, specimen source, duration of amphotericin B treatment, and concomitant medications (e.g., β-lactams, glycopeptides). Laboratory indicators include platelet count (PLT), white blood cell count (WBC), neutrophils, C-reactive protein (CRP), procalcitonin (PCT), creatinine clearance, serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and serum potassium. Note: AMB-D = Amphotericin B deoxycholate; L-AMB = Liposomal amphotericin B; ABCD = Amphotericin B colloidal dispersion. Baseline was defined as the final examination prior to the first dose.

Stratified analyses were conducted based on age, sex, underlying comorbidities, and diagnostic certainty. Statistically significant differences in effective response rates were observed among the AMB-D, L-AMB, and ABCD groups for patients aged 61–83 years, female patients, and those with a "probable" diagnostic certainty (all $P < 0.05$), as detailed in . Furthermore, significant

differences in effective response and complete response rates were found among the three groups when the duration of medication was < 3 days or > 7 days (all $P < 0.05$), as shown in .

Survival analysis results indicated that there was no statistically significant difference in the survival time associated with effective response among the three groups ($\chi^2 = 0.15, P = 0.93$), as illustrated in [Figure 1: see original paper].

Comparison of Safety

Among the 71 patients, adverse events occurred in 49 cases (69.0%). These included 31 cases of renal injury (43.7%), 18 cases of liver injury (25.4%), 9 cases of hypokalemia (12.7%), and 17 cases of thrombocytopenia (23.9%).

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0.05), as shown in Table 4 . The results of the survival analysis indicated the occurrence of renal injury, liver injury, and hypokalemia across the three groups. Diagnostic certainty Note: —indicates the use of Fisher' s exact test.

Note: Fisher' s exact test was employed for data comparisons between multiple groups.

AMB-D L-AMB ABCD P =0.93

Effective remission rate (%) Days (d) Note: AMB-D = Amphotericin B deoxycholate, L-AMB = Liposomal amphotericin B.

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Kaplan-Meier survival analysis was conducted to evaluate the effective response rates among the three groups. A hierarchical analysis was further employed to compare these rates across the AMB-D, L-AMB, and ABCD groups. Additionally, the effective response and complete response rates were compared among the three groups across different medication durations.

According to the *Chinese Journal of General Practice*, there was no statistically significant difference in survival time among patients with thrombocytopenia ($\chi^2 = 0.82, p = 0.66$; $\chi^2 = 0.21, p = 0.90$; $\chi^2 = 0.34, p = 0.84$; $\chi^2 = 2.83, p = 0.24$), as illustrated in Figure 2 [Figure 2: see original paper].

Comparison of Economic Efficiency Among Groups

The comparison of total costs and daily costs among the AMB-D, L-AMB, and ABCD groups revealed statistically significant differences ($p < 0.01$). Furthermore, the cost-effectiveness analysis demonstrated that the AMB-D regimen offers a distinct advantage, as detailed in Table 5 .

3 讨论

Currently, various formulations of Amphotericin B (AmB) are widely utilized in antifungal therapy. Although these formulations share the same active ingredient, they exhibit significant differences in their pharmacological properties. For instance, Amphotericin B deoxycholate (AmB-D) demonstrates a stronger affinity for lipoproteins; approximately 20% to 40% of AmB-D is eliminated via the kidneys and feces within one week of administration, resulting in relatively high drug concentrations in the urine.

In contrast, Amphotericin B colloidal dispersion (ABCD) and Amphotericin B lipid complex (ABLC) possess larger molecular configurations, allowing them to be rapidly sequestered by the mononuclear phagocyte system. This leads to significant drug accumulation in liver and spleen tissues while maintaining relatively low blood concentrations. Notably, ABLC exhibits superior penetration into lung tissue. Compared to other formulations, the compact particle size and anionic surface charge of liposomal Amphotericin B (L-AmB) minimize its clearance by phagocytes. Consequently, L-AmB presents superior plasma pharmacokinetic profiles and enhanced drug delivery to the central nervous system. The present study utilizes real-world data to evaluate the clinical performance of these various Amphotericin B formulations.

AMB-D L-AMB ABCD P =0.66

Incidence of kidney injury (%)

20 A

AMB-D L-AMB ABCD P =0.84

Hypokalemia incidence (%). This study evaluates the efficacy, safety, and cost-effectiveness of various amphotericin B formulations in the management of invasive fungal disease (IFD), aiming to provide evidence-based clinical decision support for the optimization of antifungal treatment regimens.

This study enrolled 71 patients, characterized by a high prevalence of underlying comorbidities, primarily renal disease, diabetes, and hypertension, which is consistent with previous reports [**?**]. Notably, our findings suggest that patients with pre-existing renal impairment were more likely to receive liposomal amphotericin B (L-AMB) treatment ($p = 0.021$). This indicates that renal functional characteristics may influence the clinical selection of amphotericin B formulations. This finding was further corroborated by the significantly higher serum creatinine levels observed in the L-AMB group ($p = 0.043$). Furthermore, *Aspergillus* and *Mucor* were the primary fungal pathogens identified in this study, aligning with the conclusions of European epidemiological studies on invasive fungal infections [**?**]. Regarding the site of infection, although there was a high detection rate in urine samples, these patients also had fungi detected simultaneously in sputum and blood; notably, no patient in this study received treatment solely based on fungal detection in the urine.

Previous literature has reported that following treatment with amphotericin B, the complete remission rate for IFD is 51%, while the remission rate for febrile neutropenia is 70.2% [**?**, **?**]. These figures are comparable to the 64.8% effective remission rate observed in the present study. No statistically significant differences in efficacy were found among the three amphotericin B formulations investigated here ($p = 0.55$). A study by Umemura et al. [**?**] found that L-AMB and amphotericin B deoxycholate (AMB-D) possess equivalent efficacy in preventing IFD following lung transplantation. Similarly, Cavassin et al. [**?**] reported on the treatment of ABLC···

AMB-D L-AMB ABCD P =0.90

Incidence of liver injury (%) Incidence of thrombocytopenia (%)

AMB-D L-AMB ABCD P =0.24

[FIGURE:A] [FIGURE:B] [FIGURE:C] [FIGURE:D]

Days (d) Days (d) Days (d) Days (d)

Note: Figure A presents the Kaplan-Meier survival analysis for the incidence of kidney injury among the three groups. Figure B presents the Kaplan-Meier survival analysis for the incidence of liver injury among the three groups. Figure C presents the Kaplan-Meier survival analysis for the incidence of hypokalemia among the three groups. Figure D presents the Kaplan-Meier survival analysis for the incidence of thrombocytopenia among the three groups.

3 组发生药物相关不良事件的 Kaplan-Meier 生存分析

Kaplan-Meier survival analysis of adverse drug events among three groups

Chinese General Practice. For the AMB-D, L-AMB, and ABCD groups (Note: Fisher' s exact test was used for comparisons between multiple groups), the overall success rate for treating invasive fungal disease (IFD) was superior in the ABCD group compared to the AMB-D and L-AMB groups. However, subgroup analysis of patients with "proven" or "probable" diagnostic certainty revealed no significant differences in efficacy among the different amphotericin B formulations. A meta-analysis of 25 randomized controlled trials similarly found no significant differences in effectiveness or mortality across the four amphotericin B formulations. These findings collectively suggest that different formulations of amphotericin B possess similar therapeutic efficacy.

In contrast to previous studies, this research innovatively demonstrates that L-AMB exhibits poorer efficacy in elderly patient populations, while AMB-D shows better efficacy in female patients. Existing literature indicates that L-AMB offers clinical advantages over AMB-D in patients with HIV/AIDS [**?**, **?**]. Based on these findings, it is recommended that clinical decision-making regarding amphotericin B formulations should comprehensively integrate patient demographics and clinical presentations. Notably, compared to other formulations, L-AMB demonstrated a higher effective remission rate ($P = 0.042$) and

complete remission rate ($P = 0.026$) within 3 days of administration, suggesting a faster onset of action.

Jadhav et al. reported similar conclusions. Conversely, AMB-D showed a higher effective remission rate after 7 days of administration ($P = 0.031$), indicating a slower onset of action. Due to its nephrotoxicity, the clinical application of AMB-D remains limited to low-dose regimens. Furthermore, pharmacokinetic studies indicate that this formulation is characterized by high protein binding, resulting in limited free drug concentrations, which may contribute to the delayed onset of action. In contrast, L-AMB allows for higher dosage regimens, is less susceptible to phagocytic clearance, and possesses a selective affinity for fungal ergosterol over mammalian cholesterol [**?**, **?**], thereby facilitating a more rapid onset. These results suggest that L-AMB should be prioritized in emergency situations requiring intensive care and rapid intervention.

Extensive research has shown that amphotericin B is associated with hypokalemia, hepatotoxicity, nephrotoxicity, hematotoxicity, and infusion-related reactions [**?**, **?**]. However, reaching a consensus on the safety profiles of different formulations remains challenging.

Previous studies have indicated that L-AMB and ABCD exhibit lower nephrotoxicity compared to AMB-D [**?**], with other reports suggesting that patients treated with L-AMB experience shorter hospital stays and lower mortality rates. Tan et al. found that the incidence of hepatotoxicity and hematotoxicity was significantly higher with ABCD than with AMB-D and L-AMB, whereas Nokura et al. reported similar nephrotoxicity between L-AMB and AMB-D. Consistent with early clinical observations, this study shows that nephrotoxicity is the primary adverse event associated with amphotericin B (43.7%), followed by hepatotoxicity (25.4%), thrombocytopenia (23.9%), and hypokalemia (12.7%), with no significant differences in adverse event rates across formulations. However, interpretation of these findings requires caution due to potential selection bias, as patients with pre-existing renal impairment at admission were more likely to receive L-AMB. Pharmacokinetic properties may explain the variations in adverse events between formulations: liposomal encapsulation facilitates targeted drug delivery to infection sites via uptake by the mononuclear phagocyte system, thereby reducing renal exposure and the incidence of kidney injury. Notably, our results show that the probability of nephrotoxicity was significantly higher than other adverse reactions across all three groups; nevertheless, L-AMB remains the recommended choice for patients with renal insufficiency. Currently, pharmacoeconomic evaluations comparing different amphotericin B formulations remain limited. Umemura et al. demonstrated that L-AMB has lower daily treatment costs than AMB-D when used for antifungal prophylaxis after lung transplantation. Conversely, Borba et al. developed a decision tree model suggesting that AMB-D is the most cost-effective option for treating invasive fungal diseases, followed by L-AMB and ABLC. Similar to the findings of Borba et al., our analysis of real-world clinical data from 71 patients suggests that AMB-D may be the most economical choice for IFD treatment.

This study has several limitations. The retrospective observational design and the single-center nature of the study may limit the generalizability of the conclusions. Furthermore, the small sample size restricted in-depth analysis of ABLC-related outcomes due to insufficient statistical power. Future research should prioritize prospective designs conducted through larger multicenter cohorts to allow for more comprehensive data collection and rigorous multivariate analysis. The results of this study provide a reference for the clinical application of amphotericin B and highlight the significance of therapeutic drug monitoring.

Author Contributions: Liu Shuai and Yuan Shichao were responsible for the implementation of the study, drafting the manuscript, performing pharmacoeconomic evaluations [AMB-D group: 975.00 (468.75, 2006.25); L-AMB group: 11505.00 (3237.50, 16962.50); ABCD group: 12276.00 (3564.00, 21780.00); $P <$ 0.01. Daily cost: 139.28 (80.20, 269.81); 1668.63 (956.09, 2638.48); 1334.35 (1018.29, 1849.09); $P < 0.01$], data collection and organization, statistical processing, and the creation and presentation of figures and tables. Liu Yan was responsible for revising the manuscript, quality control, and review. Jia Shuoxian, Zhao Yan, and Wang Ziyi participated in data collection, organization, and statistical processing. Zhou Chunhua and Yu Jing held overall responsibility for the article and provided supervision and management.

Chinese General Practice. The authors declare no conflicts of interest.

There are no conflicts of interest in this article.

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Note: Figure translations are in progress. See original paper for figures.